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U.S. National Institutes of Health

1969
annual report

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health
Bethesda, Md. 20014

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PREFACE

The National Institutes of Health, principal agency of the Federal government responsible for biomedical research, communication of biomedical knowledge, and education for the health professions, reports yearly to the public on its activities. This account always forms a part of a larger document, the Annual Report of the Department of Health, Education, and Welfare.

To permit full dissemination of information on its responsibilities and accomplishments to those with particular interest in NIH, the 1969 Annual Report is reprinted separately in this volume. Appropriate tables are appended to show appropriations, grants and other extramural awards, and personnel levels.

It is hoped this publication will serve as a ready reference source for those concerned with NIH activities.

Robert Q. Marston, M.D.

Robert Q. Marston, M.D.
Director

Officers

NATIONAL INSTITUTES OF HEALTH

as of

July 1, 1969

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Joseph Leiter	*Associate Director for Library Operations*
James Lieberman, D.V.M	*Associate Director for Audiovisual Telecommunications and Director of the National Medical Audiovisual Center*

*Denotes "Miss"

The National Institutes of Health

For the National Institutes of Health (NIH) fiscal year 1969 was a time of consolidation, new directions and of recognition for achievements of its scientists, and of hope that old threats to the Nation's health may soon be conquered.

To fulfill the intent of the April 1, 1968, reorganization of DHEW health services, NIH moved rapidly to complete its own reorganization. The Office of the Director was strengthened by addition of several key administrators. The Division of Research Grants and Division of Research Services were brought under direct supervision of associate directors of NIH. Two new research Institutes were added, one, the National Eye Institute, by congressional action, and one by the Secretary's elevation of the Division of Environmental Health Sciences to Institute status.

SPECIALIZED CENTERS

Two new specialized centers honoring long-time congressional leaders were organized and began functioning. They are the John E. Fogarty International Center for Advanced Study in the Health Sciences, named for the late Rhode Island Representative, and the Lister Hill National Center for Biomedical Communications, named for the former Senator from Alabama.

All construction grant functions of the old Division of Research Facilities and Resources, of the National Library of Medicine, and of the old Bureau of Health Manpower were consolidated within the latter, newly named the Bureau of Health Professions Education and Manpower Training. The synchronization of effort within the expanded NIH organization was enhanced when 800 employees of the Bureau were moved from Arlington, Va., to the Bethesda, Md., main campus, in March.

LABORATORY SPACE INCREASED

Room was provided for this transfer by completion of the new nine-story addition to Building 31, the general office structure. Other new facilities occupied included a new cafeteria (Building 35), and three large research buildings providing 571,336 square feet of additional laboratory space for the National Institute of Neurological Diseases and Stroke and National Institute of Mental Health (Building 36), and the National Cancer Institute (Buildings 37 and 41). Building 41, the Emergency Virus Isolation Facility, is a high security structure with unique design features.

Much of the year's change had been set in motion during the "Shannon Era," a 13-year period of NIH's greatest growth, which came to an end August 31, 1968, with the retirement of Dr. James A. Shannon as Director. The occasion brought tributes to his leadership in creating the "general excellence of the NIH operation" from scientific, educational, and governmental leaders.

SMOOTH TRANSITION

Dr. Robert Q. Marston succeeded Dr. Shannon. The agency's momentum of program effort was maintained through the period of transition and the continuing administrative regrouping.

During the year a positive effort in employee relations was instituted with the signing of an Affirmative Action Plan for Equal Employment Opportunity, to be followed up with a series of conferences and other implementing steps. Assistant HEW Secretary James Farmer hailed the NIH action as a "vanguard" measure that may point the way to improved race relations through the Federal Government.

Unprecedented recognition came to NIH during the year when Dr. Marshall W. Nirenberg, Chief of the Laboratory of Biochemical Genetics of the National Heart Institute, was named a co-winner of the Nobel Prize in Medicine, for his discovery of the key to translation of the genetic code governing synthesis of living cells and transmission of heritable traits. Dr. Nirenberg, whose entire career as a scientist was spent at NIH, shared the award with two other scientists whose work has long been supported by NIH grants, Drs. H. Gobind Khorana of the University of Wisconsin and Robert W. Holley of the Salk Institute.

FEDERAL NOBEL LAUREATE

Dr. Nirenberg is the first federally employed scientist ever to win a Nobel Prize, although another American winner, Dr. Arthur Kornberg, now of Stanford University, who won in 1959, had previously been employed by NIH. Of the remaining American winners of the Nobel Prize for Medicine or Physiology, 40 had received support from NIH for their research, it was noted.

The Nirenberg recognition was one of many for NIH scientists during the year. Among the principal ones, Drs. Earl R. Stadtman, National Heart Institute, and Bernhard Witkop, National Institute of Arthritis and Metabolic Diseases, were named to the National Academy of Sciences, bringing the total NIH membership on that prestigious body to eight. Dr. Bernard B. Brodie of the National Heart Institute was presented with the National Medal of Science in ceremonies at the White House. Dr. Robert W. Berliner, Deputy Director of NIH for Science, received the *Modern Medicine* 1969 Award for Distinguished Achievement.

In culmination of years of research gains, the year brought hopeful predictions by responsible NIH scientist-administrators that two important disease problems may soon be eliminated. In the first, a realistic appraisal of current research against dental caries suggested the possibility of complete prevention of tooth decay within another decade. In the second, it was stated that by the 1970's all of the old "normal" childhood diseases may well have "disappeared" in America.

PROGRESS EMPHASIZED

Several areas of important progress were emphasized. The first of these was better understanding of basic life processes, as evident in the work of Dr. Nirenberg, in the creation by an NIH scientist of active artificial ribosomes (protein-making units within living cells), in the synthesis of the enzyme ribonuclease by NIH-supported scientists (the first enzyme produced in a laboratory), and discovery at NIH that insulin, vital to utilization of sugar in the body, has two distinct chemical components—"big insulin" and "little insulin." Early but dramatic success in organ transplantation throughout the world was credited to extensive new knowledge developed in studies in immunology conducted or supported by NIH.

The second area of progress brought encouraging reports of effective chemotherapy in some cancers, documentation of risk factors in cardiovascular diseases, advances in the development of artificial kidneys, and better control of virus diseases by new vaccines and induction of interferon to produce greater-than-normal amounts of antiviral substances in the body.

RUBELLA VACCINE LICENSED

A third area was in making the fruits of research available to patients. Notable in this area were the evaluation of L-dopa, a drug for patients with advanced stages of Parkinsonism, and licensing of a live attenuated German measles (rubella) vaccine. Both new agents brought to fruition many years of study and testing by NIH scientists.

In addition, NIH activity moved ahead in construction and expansion of institutions for training of health personnel, assistance to students of the health professions, and encouragement given to institutions to develop new methods of teaching and curricula for new types of health personnel.

Specific accomplishments of the components of NIH are shown in the pages following.

National Cancer Institute

The National Cancer Institute is advancing the research attack on malignant disease through comprehensive studies of causative factors that may give clues to prevention and investigations to improve diagnosis and treatment. The objective is to reverse the continuing unfavorable balance of occurrence over cure, and ultimately to eradicate cancer as a major health threat.

Information essential to helping achieve this long-range objective is being gathered in the Third National Cancer Survey, covering 11 geographical regions with a total population of more than 25 million. It will include incidence rates, details of each patient's background, the economic effects of cancer, and the needs of research and medical care as they relate to all cancer cases occurring from 1969 through 1971.

Progress made toward control of malignant disease is indicated, in part, by improved survival rates, as recently reported for breast cancer. Investigators estimated that, of patients with localized breast cancer who were surgically treated in the early 1960's, 70 percent will survive for at least 20 years. This was true for only 53 percent of such patients treated in the 1940's.

CAUSE AND PREVENTION

Chemical Carcinogenesis

Scientists in search of the causes of cancer believe that it is due, in part, to many of the agents introduced into the modern environment. Hence, a reduction in the cancer problem could result from the identification of these substances and their elimination or inactivation. To this end, the Institute has launched an expanded program of chemical carcinogenesis research.

Arsenic, long known as a cause of skin cancer, has been implicated in cancer of the lung and several other sites, primarily in workers in various industries. Smelter workers regularly exposed to arsenic in the atmosphere experienced a rate of lung cancer death 3 times higher than did the general population of white men living in the same States. Those with more than 15 years of heavy exposure had an eightfold risk. The effects of exposure to sulfur dioxide in the same atmosphere must still be determined.

Pesticides are among the chemicals receiving special attention because of their potential effects on the population. A preliminary report on 120 pesticides and other agricultural and industrial chemicals studied in mice since 1964 revealed the following results, obtained under experimental conditions: 11 compounds, including DDT, caused tumors; 89 showed no tumorigenicity, and 20 gave inconclusive results and required additional investigation. Studies in other species of animals are necessary, however, before the significance of these results for man can be understood.

Oral contraceptives, too, are receiving attention because of lack of information about their long-term effects. Recent studies suggested that cancer of the uterine cervix was induced in mice by administration of an antifertility drug used for human birth control. The drug contained a type of female sex hormonal compound known as a progestational agent. Studies are in progress to determine whether there is a link between the use of oral contraceptives and human cervical cancer.

That hormonal environment may be related to certain forms of cancer was further suggested in an evaluation of cancer deaths among Catholic nuns. Chosen for study because they were unmarried and celibate, the nuns showed a striking increase in breast cancer after age 39. This is in line with earlier observations that single women experience substantially higher rates of breast cancer than do married women, and that the differential increases with advancing age. Like other unmarried women, the nuns also showed a low rate of cancer of the uterine cervix and a high rate of cancer of the uterine corpus and the ovary. Their excess frequency of cancer of the large intestine, especially after menopause, was also thought to be influenced by hormonal factors.

Relative levels of estrogen hormone fractions—estriol, estrone, and estradiol—produced 10 or so years after puberty have been proposed as possible determinants of a woman's lifetime risk of breast cancer. Administration of additional hormones to change potentially carcinogenic levels in the body might therefore be a way to prevent some of the 29,000 breast cancer deaths that occur each year. Ways to identify women who require such treatment are under study.

Smoking and Lung Cancer

The smoking of cigarettes, another source of carcinogens, is the major cause of almost 60,000 lung cancer deaths a year, primarily among men. To help reverse this trend, the Tobacco Working Group, an offshoot of the Lung Cancer Task Force composed of scientists and physicians from the Government and universities and representatives from the tobacco industry and other research organizations, is in the process of defining the technical and scientific base for development of a less hazardous cigarette. The group is concentrating on the advancement of meaningful laboratory assay systems to guide in identifying and modifying the harmful constituents of cigarette tobacco and smoke. It hopes to clarify further the relationships between smoking and health.

Viruses and Cancer

Investigations continue to link viruses with certain forms of cancer in man. Venereally transmitted Type 2 herpes virus has been suggested as a possible cause of uterine cervical cancer.

This hypothesis was tested by determining the incidence of antibodies to Type 2 herpes virus in patients with cancer of the cervix and in other population groups. Antibodies in the serum were found in 78 percent of 41 patients with invasive carcinoma of the cervix, and in 64 percent of 24 patients who had been successfully treated for the disease 4 or more years prior to the antibody test. However, antibodies were detected in only 22 percent of 51 women in a control group matched by age and race and in 35 percent of 23 women with carcinoma *in situ.* An intermediate antibody level, 54 percent, was found among a group of 43 promiscuous women, who did not have cancer.

A strong statistical correlation has been observed between occurrence of the disease and multiple sexual partners. This observation suggested that exposure to the cancer-causing agent was likely to increase with an increased number of sexual partners. The data obtained in the antibody studies support the concept of a venereal mode of spread of Type 2 herpes virus and suggest an association between this virus and cervical cancer. They do not justify at this time, however, a conclusion that the association is a causal one.

Another kind of herpes-type virus, the Epstein-Barr (EB), has been suspected of causing Burkitt's lymphoma, cancer of the lymph glands occurring primarily in African children. The virus has also been suggested as the cause of infectious mononucleosis. Antibodies to this virus were found in all African children with Burkitt's tumor, but in only about 50 percent of normal African children. In a study of Americans with no signs of the cancer, the antibodies were found in 45 percent of children 7 to 24 months old and about 75 to 94 percent of children 4 to 7 years old and of young adults. The study shows that infection with EB virus occurs early in life and with high frequency.

A virus, or some other infectious agent, may also cause osteosarcoma, a form of bone cancer. In a study of this problem in four patients, the serum of each patient contained antibodies to a common antigen (foreign material) in his own cancer tissue and those of other osteosarcoma patients. A high level of antibodies was also demonstrated in serums from members of the patients' families and close associates of one patient. A low level of the antibody found in serums from normal blood bank donors suggested that the suspected infectious agent may produce unrecognized infections in normal individuals.

Immunology and Cancer

A test under study has a potential for identifying persons with a high risk of developing leukemias and other cancers because of abnormalities such as inborn immunological defects and chromosomal disorders. These individuals can be identified by the response of their fibroblast cells, structural components of most body tissues, to a virus known to cause cancer in animals. The magnitude of their risk is related to the fraction of cells transformed by the virus in a test tube. When fully developed, the technique may also be useful for screening environmental agents for cancer-causing activity in man.

Research in the field of immunology brought to light a substance that shows promise as an anticancer agent, polyinosinic-polycytidylic acid (poly I:C). It induces the production of interferon, a protein made by cells, as a defense against viruses. When tested in tumor-bearing animals, poly I:C caused regression of the tumors, decreased rates of tumor growth, and increased survival time. Investigators are continuing animal studies of the antitumor effects of this synthetic ribonucleic acid and plan to introduce it into studies of cancer patients.

TREATMENT WITH DRUGS

Two new research subdivisions were created to aid progress in the area of chemotherapy. The Laboratory of Molecular Pharmacology was established to investigate the effects of potentially useful anticancer agents on cells and cell components, particularly at the molecular level. The Human Cell Biology Branch is directing studies on cell kinetics, the growth characteristics of populations of cells.

Encouraging results from a special leukemia study group reflect the trend toward improved survival due to the use of drugs. About 60 percent of the patients, all under 20 years of age, were surviving 24 months from diagnosis of their disease.

Further improvements in survival of leukemia victims may result from a study of eight patients with aplastic anemia. They were transfused with blood platelets from family donors whose white blood cells closely matched their own. Such compatible platelet transfusions, compared to those not obtained from relatives, were more effective, much more economical, and much safer for the patients, who showed no signs of bleeding or transfusion reactions. Blood platelet transfusion is an essential part of supportive therapy for leukemia patients, for it frequently prevents and controls hemorrhage, one of the most common causes of death among acute leukemia patients.

Advanced Hodgkin's disease, cancer of the infection-fighting organs, can be controlled with drugs to a degree not previously possible. Intensive, intermittent doses of several drugs have proved more effective than single drugs. In a study begun in 1964, a combination of four drugs induced complete remission in 35 (81 percent) out of 43 patients. Half of those who responded had remained in complete remission at the time of reporting. Other lymphomas, such as lymphosarcoma and reticulum cell sarcoma, also seem to be more sensitive to combination than to single drug therapy.

Several patients with Ewing's sarcoma, a form of bone cancer that spreads rapidly to the lungs and other organs, survived 1 to 4 years after radiation and drug treatment; the latter consisted of cyclophosphamide alone or combined with vincristine. With radiation treatment alone, most patients die within 3 years of diagnosis of their disease. Combination therapy is in a preliminary stage of development but promises continued improvement in the outlook of patients with this type of cancer.

Some progress has been made against cancer over the past year, but to be truly effective the benefits of improved diagnosis and treatment must be made available everywere. Successes achieved in childhood leukemia have been impressive but are possible as yet in only a few specialized centers. Scientists are hoping that the extension of progressive facilities will provide superior care for all leukemia patients and will serve as models for centers to provide the best treatment for patients with other forms of cancer.

National Eye Institute

Nearly every family in America has at least one member suffering some form of vision problem or eye disease. Half the people in this country wear glasses; 12 million school children need eye care. More than 30,000 Americans lose their eyesight every year. Almost 1 million persons in this country cannot read a newspaper, even with the aid of glasses. More than 400,000 Americans are legally blind and many others have such poor vision that walking and other daily activities present special problems. The National Institute of Neurological Diseases and Blindness (more recently renamed the National Institute of Neurological Diseases and Stroke) has conducted an extensive research and training program since it was organized in 1950. To emphasize further the importance of this area of research, the National Eye Institute was established in August 1968. Although a specific appropriation was not made for the new Eye Institute for fiscal year 1969, an acting Director and a National Advisory Eye Council were appointed and a series of meetings was held to determine the direction the new Institute's program will take.

No interruption occurred in current operations while the transfer of responsibilities from the NINDS to the NEI was underway. It is expected that the new Institute will have its own appropriation for the new fiscal year. All vision research and training grants are being transferred to the new Institute and the intramural and collaborative vision programs will be transferred as staff is available.

CLINICAL EYE RESEARCH CENTERS

A broad program of research in disorders of vision has been conducted at the NIH Bethesda laboratories and at grantee institutions. At present 12 clinical eye research centers are being supported.

Each center's research is focused on some particular area of the vision problem, as in the case of Washington University School of Medicine which devotes full time to glaucoma research. Other areas under intense investigation are cataract; retinopathy; infectious, inflammatory, and parasitic diseases; tumors and vascular disorders; metabolic and degenerative diseases; myopia and other refractive anomalies; strabismus, and neuromuscular disorders. In addition, collaborative and field projects and eight outpatient clinical research centers have been supported, as well as individual research and training grants.

The Model Reporting Area for Blindness Statistics now includes 16 States. Renewed efforts were made to help other States develop the required standards in anticipation of a nationwide network to provide comprehensive statistical information regarding visual impairments and blindness.

The Vision Information Center at Harvard University is now operating effectively to expedite the flow of scientific information from laboratories to eye doctors throughout the world. This Center defines, identifies, stores, retrieves, and disseminates the literature on vision.

RESEARCH ADVANCES

Some of the notable advances made through NIH conducted and supported research projects during the past year include the following:

Cataracts

Cataract surgery was made safer and easier through advancements in suture techniques, improved instrumentation, operation under microscopic control, and other technical improvements including cryosurgery. Improved preoperative medication reduced the incidence of complications. Increased evidence was found of a relationship between cataract and the way the body uses sugar, especially glucose.

Glaucoma

The need for early correction of congenital glaucoma was established and the role of diabetes in development of glaucoma in juveniles recognized. A collaborative study established means of detecting glaucoma victims through their hereditary patterns to permit earlier treatment. Advances were made in understanding the basic dynamics of intraocular pressure, in applicable diagnostic techniques, in pressure variations and aqueous humor drainage, and in understanding those parts of the brain believed to serve a pressure-regulating function. Data on the effectiveness and possibly harmful side effects of drugs used for control of intraocular pressure resulted in improved treatment.

Retinal Disorders

Much more was learned about the basic anatomy and function of the retina, especially about its general size and shape, the dimensions of the optic disk, and the relationship between the disk and the foveola.

Techniques for more successful repair of retinal detachment were increased by advances in preoperative examinations and management, surgery, and postoperative care. The laser has been used more extensively to "spotweld" the retina in certain types of retinal detachment. Cryosurgery, which removes two complications of treatment of retinal detachment (infection and scleral neurosis), is now being used in some hospitals. Surgery within the vitreous proved successful in some cases of retinal detachment where previous multiple operations failed.

Experiments resulted in development of a new method of determining exact arterial oxygen tensions associated with retinal damage, thereby insuring a better means of administering oxygen to premature infants.

New methods of freezing and dehydrating corneas for long-range storage resulted in improved corneal transplants. Stains were developed which identify changes in transplant material that might make it unsuitable for transplant, thus preventing many unsuccessful operations. Three immuno-suppressive chemicals were found which successfully delay and even suppress graft rejections in animals; these may soon be used in man. Animal tests indicated that it soon may be possible to replace scarred corneas with plastic corneas and restore sight. A single, quick procedure was developed which bonds a plastic lens to the corneal surface of the eye, improving sight in certain diseases, and protecting the cornea for further degeneration.

Tumors

Institute research revealed some promising methods for treating eye tumors, using fluorescent dyes, radioactive tracers, and the laser beam. Supervoltage irradiation in treatment of retinoblastoma (tumor of the retina) proved highly successful. Intense radiation proved effective in treating eye cancer in children. The discovery that there is often a congenital predisposition for forming harmless tumors in the eye, and that many tumors are nonmalignant, will help to save many eyes.

Other Ocular Disorders

Early treatment of congenital defects was recommended after it was discovered that the best procedures were surgery in amblyopia ex anopsia before 12 months of age, and for strabismus and congenital cataract before 18 months.

A surgical technique developed by grantees achieved improvement of visual acuity in cases of dysthyroid exophthalmos. Discovery of complications in the use of steroids in treating this disease indicates the need for careful monitoring of such treatment.

Diagnosis of the mechanism of defective color vision advanced greatly. A comparison of results of behavioral and physiological studies of the macaque and squirrel monkeys provided new insight into the mechanisms of normal and defective color vision in man.

Drug Therapy

A task force of the Subcommittee on Vision and Its Disorders probed various facets of the drug field. These studies indicated that the use of properly administered prophylactic antibiotics in eye surgery required re-evaluation. The toxic effects of a number of entities now being used were studied. Results provide guidelines for treatment that may save many eyes from blindness.

New studies of antiviral drugs were undertaken that may lead to much improved treatment of systemic virus diseases as well as eye disorders. The treatment of trachoma may vastly change due to the discovery that it is probably caused by an organism which attacks other parts of the body as well as the eye.

New Techniques and Instrumentation

The development of a more accurate mathematical model of the eye, using high speed computation, opened the door to a better understanding of its optical performance.

Sensitive new measuring devices, computers, and electronic equipment were put to use to find new ways to diagnose eye maladies. New freezing, burning, and surgical techniques were used to save diseased eyes, transplant human tissues, and implant artificial parts to save failing vision. A low voltage laser device was used at one center to discover in advance of surgery whether cataract removal can restore a patient's sight.

The clinical usefulness of electroretinography (ERG) and evoked occipitogram (EVOG) in objective evaluation of blindness in infants was demonstrated. Intravenous fluorescein was used with success in investigating four types of ocular lesions and photocoagulation used in their treatment.

Important advances continued in the analysis and correction of errors of refraction and in the design of instrumentation needed to exploit these new developments, including laser, X-rays, and ultrasound. Work continued in mapping the visual impulse through the retina and nerve pathways in the brain. Grantees found that monocular visual deprivation brought about in the activity of single cells of the cortex causes a number of neurophysiological and behavioral changes.

+ Lung

National Heart Institute

The mission of the National Heart Institute is to conduct and support research to increase scientific knowledge of the cardiovascular system; to define structural and functional abnormalities occurring with cardiovascular diseases, and to develop more effective means of prevention, diagnosis, and treatment.

EXTRAMURAL PROGRAMS

The backbone of the Institute's activities in fulfillment of this mission is its large, diversified research grants program, which, during fiscal year 1969, supported nearly 2,000 research projects at universities, medical schools, and other institutions throughout the United States.

Many of these studies yielded basic information on the cardiovascular system, the blood, the lungs and kidneys, and the endocrine glands, whose secretions influence cardiovascular performance. Other grant-supported studies developed information, techniques, and instrumentation directly applicable to clinical problems posed by the cardiovascular diseases: for example, there were clinical trials of promising new drugs, improved diagnostic procedures, improved surgical and life support techniques, and improved monitoring and treatment procedures for acute heart attacks and other consequences of heart and blood-vessel diseases. And still other studies, ranging from animal experiments to epidemiological investigations of human populations, explored factors that increase susceptibility to cardiovascular diseases.

Atherosclerosis and Coronary Heart Disease

During the past year the Institute has undertaken a detailed analysis of selected research areas in its grants program. The aim is to strengthen the search for means to prevent atherosclerosis and its complications.

Of crucial importance is fuller understanding of the underlying causes of atherosclerosis; of the mechanisms by which it attacks the arterial wall, and of factors increasing susceptibility to the disease, accelerating its development, and precipitating its disabling or lethal complications. A heart attack or stroke is a culminating event of a disease process that has been going on for many years. Can it be prevented from starting at all? If the process is already underway, can therapeutc intervention retard, arrest, or reverse its course, or prevent the development of heart attacks or strokes?

One possibility is that the reduction of blood lipid levels by diet, or other means may reduce susceptibility to atherosclerosis, and also the risk of such consequences as heart attacks.

Earlier feasibility studies demonstrated that palatable diets can be devised that will bring predictable reductions in blood cholesterol. Not yet established is whether such diets, if followed by large groups of people for prolonged periods, will affect morbidity and mortality rates from coronary heart disease. A test of this hypothesis has been suggested and is under study by the Institute. A 12-member Diet-Heart Review Panel was convened to examine various approaches. The possibility of conducting a study in an open, free-living population is still under consideration, but it also appears that an equally definitive study might be made at much lower cost and with more adequate controls among institutionalized subjects. One small grant-supported study is already underway and might be expanded, by gradual addition of similar study groups, to achieve the numbers required to demonstrate any effect of dietary modification on coronary heart disease experience.

Another large field trial, whose object is secondary prevention, is the Coronary Drug Project. This study is designed to determine whether and to what extent lipid-lowering drugs will confer protection against recurrent heart attacks and other complications in men who have previously experienced one or more heart attacks. The goal is to reduce by 25 percent or more the existing 5-year mortality rate among treated subjects at the highest risk of death from coronary heart disease.

The drugs being evaluated are nicotinic acid, dextro-thyroxine, clofibrate, and conjugated equine estrogens at two dosage levels. Patients in each of the five treatment groups will be compared with a control group which will receive a placebo rather than drugs, but will otherwise receive the same care as the treated patients. The study is underway at 55 participating clinics. Patient recruitment was completed in June of 1969, and the clinical phase of the project will be completed in 1974.

In addition to its regular research grants program, the National Heart Institute carries on several special research and development programs. Supported for the most part through contracts, these are directed against specific, well defined health problems.

The Artificial Heart Program

This program, which began operations in 1964, is seeking to develop devices and techniques for providing temporary or permanent assistance to a failing circulation and a total replacement for hearts damaged beyond salvage. More than $26 million in contracts have been awarded to attack specific bioengineering, physiological, and related problems of artificial heart development.

During fiscal year 1969, the program supported more than 100 contracts, totaling more than $7 million, in such key areas as instrumentation, materials development, and evaluation, implantable and external power sources and control mechanisms, new circulatory assist devices and blood oxygenators, various physiological problems of assisted circulation, and test and evaluation facilities.

In June 1969, the program sponsored a 5-day Artificial Heart Conference in Washington, D.C. The conference featured 90 presentations by scientists conducting research under contracts from NHI. The Conference Proceedings, will be published later.

The NHI Task Force on Cardiac Replacement, convened by the Director, NHI, in November of 1968, met several times to consider medical, social, and economic problems surrounding the replacement of hopelessly diseased or damaged human hearts with heart transplants or with mechanical devices. The 10-member group was charged with making recommendations to the Institute concerning foreseeable program needs.

The final report, yet to be submitted, will cover the current medical and technical "state of the art" in heart transplantation and artificial-heart development; present and projected costs of heart replacement procedures and potential sources of payment; present and projected requirements for trained personnel and suitable facilities for the preoperative, operative, and postoperative care of candidates for heart replacement; social, ethical, and moral problems raised by the possibility of heart replacement, and research needs for the solution of technical problems posed by heart transplantation and the development of clinically acceptable artificial hearts.

The Myocardial Infarction Program

This national program of biomedical research directed against acute heart attacks, complements the Artificial Heart Program and provides medical knowledge useful in development and evaluation of circulatory assist devices and techniques. It is in the treatment of heart attack victims that these devices are likely to achieve their greatest potential.

A principal element of the program has been the establishment of a chain of Myocardial Infarction Research Units (MIRUs) combining unexcelled patient care with intensive clinical and laboratory research on acute heart attacks and their complications.

During the year, new MIRUs were established at the University of California, San Diego; Cedars-Sinai Medical Center, Los Angeles; the University of Chicago, and the University of Rochester. In addition, the Myocardial Infarction Program continued support for MIRUs previously established at the University of Alabama, Cornell, Duke, and Johns Hopkins Universities, and Massachusetts General Hospital.

Thrombosis and Hemorrhagic Diseases

Another important sector of NHI research is thrombosis and hemorrhagic diseases. Thrombosis is important because clots or emboli are responsible for the great majority of heart attacks, more than half of all strokes, and for many other serious consequences of blood-vessel diseases. Thrombosis also complicates use of artificial valves and other cardiovascular prostheses.

Specific goals of projects underway or planned for the immediate future include:

- Development of automated procedures for large-scale production of plasma and cellular fractions (red cells, white cells, platelets) from whole blood.
- Development of high-yield techniques for fractionating plasma to yield albumin, gamma globulin, blood-clotting factors, and other protein fractions.
- Investigation of chemical additives and freezing techniques for preservation of whole blood and blood components.
- Studies of the feasibility of computerized local, regional, or national inventory systems for blood donors and blood products.
- Study of hypercoagulability states possibly induced by certain contraceptive drugs.

The program is also supporting a cooperative clinical trial in 18 institutions of the clot-dissolving drug urokinase for use against pulmonary embolism.

THE INTRAMURAL RESEARCH PROGRAM

This program blends basic research on the structure and functions of the cardiovascular system with clinical research directed against specific cardiovascular disease. Some accomplishments of this program that generated scientific interest during the year include:

- Implantation in a dog of a nuclear-powered pacemaker developed by AEC. The implantation was the first in a series of experimental implantations to establish the total reliability of the pacemaker, which is designed to last 10 years or more.
- An "artificial placenta" system, featuring a blood oxygenator also developed by NHI, that shows considerable promise in sustain-

ing premature infants, especially those suffering from hyaline membrane disease.

- Clinical studies on the effects of the hormone thyrocalcitonin, the metabolically active form of vitamin D (25-hydroxycholecalciferol), and other therapeutic measures in the treatment of disorders of bone metabolism.
- Studies clarifying the effects of certain steroids from the adrenal glands, certain trace metals, vitamin A, and compounds called thiols and thiol-containing drugs on taste and smell thresholds.
- Development of a technique employing gas chromatography to analyze amino acid products resulting from the sequential breakdown of peptides, thereby making feasible a completely automated procedure for determining the chain structure of proteins.

Of the numerous honors and awards received by NHI staff members during the year, one was of special significance:

- Dr. Marshall W. Nirenberg, Chief of the Laboratory of Biochemical Genetics, became the first Federal scientist to receive the Nobel Prize. He was honored for his research on the genetic code.

National Institute of Allergy and Infectious Diseases

VACCINE DEVELOPMENT

Since one of the research missions of the National Institute of Allergy and Infectious Diseases (NIAID) is to develop new knowledge on communicable illnesses posing threats to human health and life, the completion of successful rubella (German measles) vaccine field trials and subsequent licensing of a vaccine for commercial use were high points in fiscal year 1969.

In February at an International Conference on Rubella Immunization, cosponsored by NIAID, the Division of Biologics Standards (DBS), and New York University, scientists from more than 25 nations reported their findings and observed what the conference chairman characterized as "the beginning of the end" of a disease which—though mild in children and most adults—often cripples the unborn of mothers susceptible to rubella virus.

Persons at the other end of life's spectrum—the elderly—will share with the very young expected benefits of NIAID's pneumococcal pneumonia vaccine program. Following contract-supported surveillance studies which identified the pneumococcal bacterial types most prevalent and the population groups at highest risk of infection, the NIAID has awarded a contract to a drug firm to produce experimental pneumococci vaccines. After safety testing, these will be ready for clinical trials in selected high-risk patients in the fall of 1969. Large-scale vaccination trials are not anticipated for another year or two.

INFLUENZA

Although bacterial complications, such as pneumococcal pneumonia, are the principal killers during influenza epidemics, a new antigenic variant of influenza A2 virus attracted worldwide attention. The disease it caused, known as the "Hong Kong flu," spread rapidly from the Far East to the United States and Europe.

The appearance of this new strain offered an unprecedented opportunity to study the influenza virus in an immunologically inexperienced population. Because NIAID had had its large collaborative vaccine development program in progress for several years, it had the necessary facilities immediately available. With little expenditure, existing contracts were extended to cover evaluation of highly purified Hong Kong influenza vaccines. Protection afforded different age groups is being compared, and improved ways of administering influenza vaccines are being investigated.

The unusual ability of influenza A to mutate to strains, such as the Hong Kong variant, focused attention on the importance of virus genetic studies which might lead to better methods of control. In November, NIAID and Rutgers University sponsored at Princeton, N.J., a workshop on influenza genetics. A number of investigators suggested that the high incidence of influenza infections in various domestic and wild birds and animals might indicate that epizootics constitute reservoirs of influenza strains that can undergo abrupt mutations culminating in epidemic infections of susceptible human populations.

INTERFERON

Turning from vaccines to other protective methods, NIAID scientists made considerable progress during the year in extending scientific knowledge of the ability of interferon—a naturally occurring body substance—to control viral and other infections. In November it was reported that an interferon inducer—a chemical known as polyI: polyC—had been used to cure a serious eye infection in rabbits. Interferon induced by polyI:polyC applied as late as 3 days after onset of infection was 100 percent effective—a startling finding when one considers that most viral infections in animals or man are impervious to presently known drugs. This research has now been extended—with similar good results—to other viral infections of laboratory animals, including influenza.

Interferon research, using polyI: polyC, led NIAID scientists, in collaboration with National Cancer Institute investigators, to test this chemical's effect on animal tumors. Results were so encouraging that toxicity studies of polyI: polyC are now in progress prior to careful testing of the compound's effectiveness in treating malignant disease in man.

IMMUNOLOGY

Expansion of the Laboratory of Immunology in the intramural program and recruitment of an outstanding scientist to serve as chief provide evidence of the Institute's continuing interest in basic immunology studies which undergird investigations of allergic conditions.

In addition, for several years, a Transplantation Immunology Branch has administered a contract program directed toward improved results in organ transplantation. In a year when public interest in transplant operations reached an alltime high, laboratories operating under contract to NIAID carried out tissue typing—a technique whereby donor and recipient tissues are matched as closely as possible—for 62 heart, 13 bone marrow, 3 pancreas, 592 kidney, and 13 liver transplants. Of particular interest, NIAID funds and facilities were used to type most of the 65 heart transplants performed as of March 1969 in the United States. In fact, a single contractor typed 42 of these, or 65 percent.

Other research supported by NIAID contracts, as well as by grants, has been devoted to developing immunosuppressive measures for reducing the body's rejection response, and to meeting the problem of organ preservation. Success in the latter objective will buy time needed to match donor and recipient tissue and will help balance supply with demand geographically.

A number of NIAID-related meetings in the field of immunology were held during the year. The Second International Congress of the Transplantation Society met in New York City in September with NIAID support. Two workshops on immunological tolerance and on mediators of cellular immunity were sponsored by the extramural program of the Institute. At all of these meetings, the Institute's goal was to foster productive development of immunology, particularly in the area of scientist-to-scientist communication.

CLINICAL STUDIES

Of special clinical interest during the past year is the progress which has been reported in oral treatment of cholera. A field trial of oral therapy, planned by scientists at the Pakistan-SEATO Cholera Research Laboratory, whose program is sponsored by the Agency for International Development and by the National Institutes of Health, was carried out under epidemic conditions. Oral therapy alone cured patients with mild disease and, in others, the amount of intravenous fluid needed was reduced by 70 percent. This means that even in remote areas, effective cholera treatment can be provided at reasonable cost.

In the Panama Canal Zone, at NIAID's Middle America Research Unit, scientists reported progress in the development of immunologic methods for distinguishing Machupo antibodies from those induced by other viruses of the Tacaribe group. Machupo virus causes Bolivian hemorrhagic fever, a disease which ravaged areas of South America several years ago. Several other members of this new group of viruses are being investigated for their importance as a cause of human disease.

At the National Insitutes of Health's Clinical Center, NIAID has initiated a limited program on aspirin hypersensitivity. Eventually these studies will be expanded to include patients with other drug reactions. In addition, of increasing interest to a number of NIAID physicians are a variety of diseases characterized by an abnormal immunological response.

National Institute of Arthritis and Metabolic Diseases

Few afflictions cause as much misery as the chronic diseases that are the concern of the National Institute of Arthritis and Metabolic Diseases (NIAMD). Because basic studies of the nature and modes of action of these disorders offer the greatest hope of eradicating them, the Institute has an important stake in conducting and supporting research in fundamental sciences such as biochemistry, enzymology, molecular biology, histology, pathology, pharmacology, toxicology, and genetics.

Arthritis alone, which comprises a group of diseases characterized by inflammation and impairment of the joints, afflicts about 16 million Americans. The metabolic diseases, characterized by a specific usually inherited, disorder in body chemistry, include diabetes, which affects about 4 million Americans, and cystic fibrosis. In addition, for years the Institute has accepted an even broader challenge, bringing its resources to bear in research on diseases of the digestive system, such as peptic ulcer and ulcerative colitis; liver diseases; disorders of blood, bone, and kidney; urology; orthopedic surgery; skin diseases such as psoriasis; endocrine disorders, and nutrition.

ARTHRITIS

Experimental evidence continues to suggest that an obscure infectious process may be involved in the causation of rheumatoid arthritis. In previous studies, investigators had produced arthritis in monkeys by injecting them with *Bedsonia* viruses isolated from human patients with Reiter's syndrome, a disease related to rheumatoid arthritis. New studies now have shown that *Bedsonia* viruses infecting the rabbit eye will disseminate to joint tissues, liver, kidney, and spleen, in a manner suggestive of major organ involvement in human rheumatoid arthritis.

A new corticosteroid drug, triamcinolone hexacetonide, has been found to combine the important features of rapid and prolonged action with minimal side effects on long-term repeated use. The response to the drug by 58 patients with rheumatoid arthritis and by eight patients with osteoarthritis was judged excellent.

A promising technique utilizing immunofluorescent staining of skin biopsies has been devised for the diagnosis of systemic lupus erythematosus in its early stages. Tests on 45 of 50 affected patients were positive and the total time required for the test was 24 hours. It is believed that sufficient differences exist between positive and negative results to develop a useful diagnostic test for this serious connective tissue disease.

DIABETES

Basic laboratory research has revealed the presence of a heretofore unknown precursor form of insulin, termed "proinsulin," in the human pancreas. This substance has been found to have very little biological insulin activity, and indications are that it may function primarily as a necessary intermediate in the proper assemblage, in the pancreas, of the active insulin molecule. Thus, a partial or complete failure of proinsulin conversion to biologically active insulin may account for some form of diabetes. Concomitantly, insulin has been shown to exist in two distinct forms in man: "little insulin," which is indistinguishable from the hormone produced by the pancreas, and "big insulin," which is a larger molecule and comprises up to 50 percent of the insulin in the circulation. The physiology of insulin secretion is being reexamined in light of these new findings.

Clinical studies have shown that a new oral antidiabetic drug, glycodiazine, significantly reduces elevated blood sugar levels in patients with maturity-onset diabetes and maintains blood-sugar concentrations at safe levels as long as the drug is administered. There were no untoward side effects associated with the drug's use and long-term clinical trials are underway to evaluate the safety of this promising new oral antidiabetic agent.

Other investigators have demonstrated that alcohol augments the hypoglycemic effect of insulin, and that excessive use of alcohol by insulin-dependent diabetic patients may result in severe hypoglycemia and irreversible, sometimes fatal neurological changes.

CYSTIC FIBROSIS AND OTHER METABOLIC DISEASES

Using staining techniques to study cultured skin fibroblast cells, a newly discovered difference has been found between cells of normal persons, patients with cystic fibrosis, and symptom-free carriers of the genetic trait for cystic fibrosis. Besides providing a reliable method to identify carriers, the procedure may permit study of the molecular basis for this disease. It has also been shown that adult males with cystic fibrosis are infertile due to anatomical lack of vas deferens, the duct which transports spermatozoa from the testes. It thus appears unlikely that the adult male with cystic fibrosis can reproduce, a fact which should be taken into consideration in genetic counseling.

Another new laboratory technique has provided a means of identifying children with certain hereditary metabolic disorders *prior* to birth. This technique can be applied in cases of a pregnancy where there is likelihood that the developing fetus may have inherited a grave metabolic disorder (as when siblings are known patients afflicted with the disease, or the parents are known carriers). The procedure involves drawing of a sample of the amniotic fluid in which the growing fetus is immersed *in utero*, and culturing the fetal skin cells which can be isolated from the fluid. Small quantities of these cells may then be tested to see whether they exhibit the biochemical abnormalities characteristic for the suspected disease.

Using this method, an unborn female child has been identified prior to its birth as a symptom-free carrier of the trait for Lesch-Nyhan disease, a tragic disorder marked by brain damage, excessive production of uric acid, and an early death. A similar technique was employed to make prenatal diagnoses of the Hurler and Hunter syndromes in the developing fetuses of two women who had previously borne children affected with one or the other of these disorders. This new technique of culturing fetal amniotic cells and testing them for suspected biochemical defects (when parents are known carriers of a metabolic disease) should lead to more effective genetic counseling.

In a related study, the Hunter syndrome has been attributed to deficiency of an enzyme involved in mucopolysaccharide metabolism, which is deranged in this disorder.

KIDNEY DISEASE AND TRANSPLANTATION STUDIES

Progress in developing a new, compact, highly efficient, and disposable artificial kidney has been made under a contract from the Institute's Artificial Kidney Program. The "capillary kidney," so-called because it simulates the human kidney's network of blood capillaries, consists of approximately 11,000 hollow, hair-size cellulose fibers packed into a case about the size of a large flashlight. The new dialyzer requires no blood pump and very little blood to prime it, thus eliminating the need for compensatory blood transfusions (and their attendant hazard of hepatitis). It comes pre-sterilized, ready-to-use, and may be re-used several times. Scores of patients with chronic kidney failure have now been maintained for periods of several months using only the new capillary kidney.

Meanwhile, a method has been devised for preserving excised human kidneys as long as 17 hours prior to final transplantation into a patient by using a transportable organ preservation machine. This makes possible the salvaging of human kidneys in cases of fatal accidents or expected hospital deaths for transplantation. Other workers have successfully transplanted a thymus gland into a male infant born without this gland, which is believed to be involved in the body's normal antigen-antibody reactions and in initiation of normal lymphocyte production in infancy. The child is now growing normally and is no longer suffering from unusual infections.

Complete or partial remissions have been achieved in 11 of 15 children with the nephrotic syndrome following treatment with the immunosuppressive drug azathioprine. In addition, growth spurts were observed in several of these children with growth retardation secondary to previous adrenocorticosteroid therapy.

GASTROENTEROLOGY AND NUTRITION

In previous studies, the stomach hormone gastrin, which stimulates secretion of gastric juices, was isolated and synthesized. Gastrin has now been shown to reside within particular cells of the antral pyloric glands, a finding which should further stimulate peptic ulcer research.

In nutrition research the principal biologically active form of vitamin D has been isolated in pure form. Preliminary tests of its ability to prevent or cure rickets in animals have shown it to be markedly more effective than vitamin D itself, suggesting that the newly discovered substance may be superior to the conventional vitamin in the treatment of rickets and, particularly, in the treatment of conditions heretofore labeled as "vitamin D-resistant."

HEMATOLOGY

Aplastic anemia is a grave, and eventually fatal blood disorder in which the blood marrow fails to produce adequate amounts of essential cellular blood elements. Preliminary trials of oxymetholone, a synthetic derivative of the male hormone testosterone, have indicated that it has value in treating children with aplastic anemia who do not respond satisfactorily to conventional drug therapy. Furthermore, a new type of usually fatal aplastic anemia following infectious hepatitis has been described. Sixteen cases of the syndrone have been reported thus far and indications are that the syndrome may result from hepatitis virus-induced chromosomal damage to the bone marrow.

FILMS AND PUBLICATIONS

"Gift of Life," a film produced by the Institute staff for the public, describes the use of artificial kidney machines in the home and points up the progress being made by the Institute's Artificial Kidney Program. Prints of the film are available on loan from the National Medical Audiovisual Center.

A new bi-monthly professional current-awareness (or alerting) publication developed by the Institute, *Endocrinology Index*, facilitates communication, integration of research and clinical efforts, and literature retrieval in the field of endocrinology. Three new publications were prepared by the Information Office—"Gout", "Arthritis and Research", and "National Institute of Arthritis and Metabolic Diseases." The latter reflects the scope of investigations conducted by the Institute and, like the other two pamphlets, is intended for general distribution.

National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) sponsors and conducts research and training in areas relating to maternal health and human development, focusing not on any one disease or part of the body but on the continuing process of growth and development, biological and behavioral, from reproduction and perinatal development, through infancy and childhood and on into maturation and aging.

Institute research is concerned with the health of infants, children, adults, and aged persons, and the causes and significance of biological and behavioral changes in both normal and abnormal aspects of human development. Its range of interest includes not only biomedical investigations but social issues as well, such as the effect of cultural changes on the personality of individuals, the rapidly expanding population, infant mortality, the effect of a mental retardate on the family structure, and the problems faced by the aged.

Among the Institute's largest research efforts in fiscal year 1969 were investigations into:

- Population problems—including demographic studies and studies to develop an array of contraceptive methods which are effective, safe, reversible, inexpensive, and suited to the diverse requirements of the world's varied population groups.
- Poor nutrition, and how this affects the childbearing woman and her progeny.

- The disease conditions of infancy—blood incompatibility caused by the Rh factor, respiratory distress in the newborn, the sudden death of apparently healthy infants in the first few months of life.
- The lifespan of individuals and generations—the biological and behavioral consistencies and inconsistencies within the individual and between generations in the same family.
- Mental retardation—its causes, prevention, and treatment.
- Human behavior, both normal and abnormal.

CENTER FOR POPULATION RESEARCH

The Center for Population Research was established and a Director appointed in August 1968. The center has two primary functions: (1) to organize and direct a contract program in population research, carried out by the Contraceptive Development and Behavioral Sciences Branches, and (2) to be the focus of coordination and information for the variety of population research efforts throughout the Federal establishment.

Concerned with the need for an array of safe, inexpensive contraceptives that are acceptable to the world's varied population groups, the center awarded over 70 contracts to support studies in reproductive biology which seemed most likely to lead to the development of new methods of contraception. Since the total amount requested exceeded the funds available to the Center for Population Research, a transfer of $1.5 million of Agency for International Development funds to the Institute was arranged. These additional funds have made it possible to support all of the approved contracts in the four areas of investigation selected as being particularly promising. These are: (1) maturation of fertilizing capacity of spermatozoa; (2) oviduct function and gamete transport; (3) corpus luteum function and implantation, and (4) the biology of pre-implantation ovum. The center also supports contracts exploring the medical effects of the oral contraceptives and intra-uterine devices, and the behavioral aspects of population research such as population structure, family structure, trends in fertility, and childbearing patterns.

INTRAMURAL ACTIVITIES

The accomplishments of the scientists in the Institute's Gerontology Research Center have been significant. Specific changes in learning capacity with aging have been identified which indicate that older individuals are unduly confused by irrelevant information. A novel enzymatic pathway for active transfer of glucose across cellular membranes has been discovered by center scientists. This finding is a possible explanation for the mechanism of glucose resorption into the body.

In other Institute laboratories, scientists have identified, documented, and studied the first human example of complete absence of an autosomal chromosome, a unique and important accomplishment. Previously, absence of an autosomal chromosome was thought to be incompatible with life. A comprehensive study of the electrical characteristics of the fetal heart and brain has demonstrated the sensitivity and usefulness of this method for evaluating fetal distress. A study of alterations in estrogen excretion of subhuman primates has led to the discovery that the peak of estrone excretion is closely related to the predicted time of ovulation by timed observations of the ovaries.

Significant Publications

During the year, the Institute published and distributed a number of books and reports, the titles of which are indicative of the wide range of activities and interests within its scope. These publications include: *Optimal Health Care for Mothers and Children: A National Priority; The Retirement Process; Contributions of Subhuman Primate Research to Understanding Human Development; The Social Sciences and Mental Retardation: Family Components; The Effect of Differences in Curricula and Experiences on Social Work Student Attitudes and Knowledge About Mental Retardation; Perspectives on Human Deprivation; The Reading Process; Current Population Research, 1966; Bibliography of Gonadotropins for 1966; Adult Development and Aging Abstracts.*

EXTRAMURAL ACTIVITIES

The Institute is currently supporting approximately 1,400 extramural research and training projects in the amount of $53 million. This represents 100 fewer projects than were reported during the last fiscal year for the same amount of funds and represents a continuing general trend toward gradually increasing the average annual commitment per grant. While the number of research grants decreased, the number of contracts funded increased almost 300 percent, from 44 in 1968, to 117 in 1969. This increase is represented primarily by contracts supported by the Center for Population Research.

Population Problems and Reproductive Biology

Analyzing U.S. mortality trends since 1951, a scientist at the NICHD and his colleague at the NINDS found evidence to support the recent British finding that the incidence of thromboembolic disease in women during their reproductive years is increased for those who have used oral contraceptives.

Such evidence that oral contraceptives might not be as safe as once thought, together with concern about the burgeoning population, make the development of new contraceptives imperative.

A positive and simple means of detecting the time of ovulation in women would provide one means of birth control which would be acceptable to religious groups which object to any mechanical interference with conception. An Institute-supported investigator is approaching the detection of ovulation through an immunochemical detection of luteinizing hormone (LH) in the urine. His study of 106 menstrual cycles of 43 normally menstruating women shows the immunochemical detection of LH in the urine as a reliable guide to the approximate time of ovulation. If the detection technique can be perfected, it will be useful in problems of infertility, as well as birth control.

One investigator supported by the Institute has found that among infertile couples without demonstrable organic cause for infertility, a remarkable percentage of females possessed circulating antibodies capable of agglutinating human spermatozoa. If a means can be found to control this immunologic infertility, it could be used as a means of contraception as well as being helpful to couples now unable to have children.

Perinatal Biology and Infant Mortality

Emphasis is being placed on the respiratory distress syndrome and hyaline membrane disease, which cause the death of a large number of infants. A grantee of the Institute has devised a method of monitoring fetal heartbeats, even during the contractions of the uterus. The development of this procedure has resulted in a 75 percent drop in the incidence of primary caesarian sections in the obstetric service of the Yale University Medical Center, where it was devised.

Atelectasis, the collapsed or airless state of all or part of the lung is the hallmark of hyaline membrane disease and may be the only manifestation in some infants who die within a few hours of birth. Recent findings of an Institute-supported investigator at Johns Hopkins University suggests that a low concentration of fatty acids in the secretions of the lungs of these babies may be responsible.

Research on the Developing Years

Nutrition and the problems of malnutrition continued to receive emphasis, paralleling the increased national interest in the subject. Long-term field studies being supported in Guatemala, where isolated villages provide a suitable environment, have demonstrated, in preliminary findings, the existence of marked nutritional deficiencies in pregnant women and young children, reflected in alterations in placentas, poor and distorted physical growth of youngsters, and high mortality rates.

The results from this carefully controlled, comprehensive long-term study are expected to yield important information about the effect of nutrition.

Results in Aging Research

Studies of changes in human amnion cells, harvested from the placenta, are making important contributions to our knowledge of the biology of aging. Institute supported investigators have previously used amnion cells to investigate metabolic changes with age. Because division seems to refresh cell functioning, the investigators believed that cells that could be kept nondividing would show aging most clearly. The only type of human cell that can be kept nondividing in tissue culture long enough to probe for aging is the amnion cell. Attributes of this cell type are homogeneity of cell population and low rate of cell degeneration. Dramatic age-dependent changes noted in the amnion cells included a decrease in cell density with age, a decrease in DNA synthesis, and an increase in incorporation of free fatty acids and cholesterol into cell lipids.

Research in Mental Retardation

The Institute is charged with supporting a major portion of the research and research training which is being conducted and will be conducted in the 12 Mental Retardation Research Centers authorized in 1963. Fresh approaches to the problems of mental retardation and psychosocial deprivation have been developed.

At the University of Kansas, the problem of cultural deprivation has been approached in a novel way. The principal investigator has developed a program of preschool education, remedial training, and parental guidance within a public housing project. Using positive reinforcement—praise and approval—as a primary tool, the investigators have sought instructional programs for teaching basic educational and social skills to these children. In addition, parents have been taught to use positive rather than negative reinforcement in training their children.

An Institute grantee who is studying gestational anomalies has recently found serious brain and skull defects in four fetuses from LSD users who had therapeutic abortions, and in the spontaneous abortus of a fifth patient. He has examined tissue specimens from 482 spontaneous abortions and 247 selected therapeutic abortions for evidence of chromosome anomalies which may have caused early damage to the fetus.

These and other studies which pinpoint the cause of birth defects do much to reduce the incidence of mental retardation.

National Institute of Dental Research

PREVENTING TOOTH DECAY

Caries (tooth decay) today is developing at three times the rate that dentists can repair it. The mammoth dimensions of this problem and the growing demands for dental care have spurred an intensified search for preventive measures directed at the complete prevention of caries within a decade. This targeted program, launched by the National Institute of Dental Research, is expected to accelerate the flow of new materials and techniques from the laboratory of the basic scientist into development and testing.

Among the exciting assortment of materials now emerging is a "baggie" type of film. Early experimental tests have shown that it may be possible to protect children's teeth from decay by applying a thin, invisible plastic coating once or twice a year. Developed originally to seal the pits and fissures in the chewing surfaces, the film may prove beneficial to the entire tooth.

A fruit-flavored fluoride tablet also shows promise in combatting decay. Tests with first-, second-, and third-grade school children show that the daily chewing of a tablet over a 2-year period reduced caries by 23 percent. This treatment would require no dental professional time.

The most common site for tooth decay is in the pits and fissures of chewing surfaces, where bacteria and food are trapped by the terrain. In contrast, decay on the smooth surfaces is attributable to the presence of bacterial plaque. Saliva would wash bacteria off the smooth surfaces, were it not for the secretion by certain streptococci of a sticky polysaccharide material, an insoluble form of dextran. All sorts of bacteria can become stuck in this glue. This year it was learned that one very common mouth organism, *Veillonella*, which does not make plaque on a clean tooth, can, however, greatly add to its accumulation once streptococci have deposited an initial adhesive film of plaque.

RESTORATIVE MATERIALS

The search for new materials is not only to improve restoratives for fillings but also to meet other oral health needs. This year, NIDR-supported scientists developed a promising cobalt alloy for making clasps to anchor dentures to adjacent teeth. The greater ductility and softness of the new alloy should reduce breakage, cause less wear on the natural teeth, and require less of the dentist's time to grind and adjust dentures for a proper fit.

Another advance comes from Institute-supported metallurgists who have discovered a new technique for strengthening a gold-nickel alloy with metal fibers. The alloy has potential use in orthodontic wires, denture clasps, and castings for inlays.

PERIDONTAL DISEASE

New evidence suggests that a physiologic gum-to-tooth attachment forms a barrier to periodontal (gum) disease. Special attachment structures at the cell membrane have been found in epithelial cells which line the gums. Studies with the electron microscope have shown that a cementing substance is discharged through the membrane. Tissue culture techniques employed in these studies may help scientists find ways to promote reattachment of gums to teeth.

Other research approaches are also being made. One focus is on the endotoxins, poisonous substances released from the cell walls of many microorganisms when they die. It appears that endotoxins do not activate the changes leading to periodontal disease because they do not penetrate normal gum lining. However, once this membrane is damaged, endotoxins can enter and aggravate destruction in the underlying tissues.

GROWTH AND DEVELOPMENT

In some individuals with extreme malocclusion, the chin and lower jaw protrude far enough to cause open bite and overlapping of upper teeth by the lower ones. Until recently, little was known about the nature and permanence of the resulting adjustments which take place in the hinge (temporomandibular joint) region. Development of a new technique of X-ray visualization by an NIDR grantee showed that surgical treatment of malocclusion is anatomically as well as esthetically successful. Even in middle-aged adults, the jawbone appears capable of remodeling and growth in response to stress.

This year a way was found to distinguish the rare, painless, and often familial jaw tumors of cherubism from confusingly similar giant-cell tumors. In all of the cases studies, the microscope showed deposits of collagen in the shape of "cuffs" around the smallest (capillary) blood vessels. Accurate diagnosis is essential for proper treatment of this condition since it is due to a dominant gene and not a malignancy, and regresses after puberty. Therefore, surgery is necessary only when overgrowth interferes with eating or talking.

Because teeth come in two sets, beginning when the embryo is about 6 weeks old and continuing in the case of wisdom teeth until about age 15, some of them are in a vulnerable embryonic condition over a far longer period than any other tissue. Therefore, scientists who know the normal patterns of eruption and shapes of teeth believe that particular tooth defects can reflect the effect of a particular health hazard and pinpoint the time of occurrence. NIDR grantees found that abnormally shaped teeth are much more common in severely retarded children than in the general population, and that deformities associated with mongolism, for example, differ from those associated with other forms of retardation.

ANESTHESIA

Ever since a dentist first brought ether anesthesia to the public, research in pain reduction has been part of dental science. This year, NIDR-supported studies showed that, by adding a small amount of a soluble dextran to a local anesthetic used to control pain following an operation, it is possible to increase the pain-free period safely by many hours without causing physiological depression. This procedure avoids the problems of drowsiness, nausea, and depression of the cough reflex usually associated with narcotics. These are serious hazards to a clear airway when, for example, jaws have been wired together for the treatment of fracture.

CLEFT PALATE STUDIES

New insights into problems of cleft palate children were provided this year. Grant-supported surgeons reported that the usual middle-ear infections which lead to deafness in these children can be largely prevented by removing adenoids at the time (usually about 3 months) when the palate is repaired.

In the absence of physical impediments to speech, behavioral problems were frequently found to be associated with speech difficulties in cleft palate children. In such cases, it was determined that psychological help is more essential than speech training.

National Institute of Environmental Health Sciences

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biological factors in the environment that can adversely affect man; to learn how these operate, and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods; the interaction of multiple agents resulting in enhanced effects, and the modifying effects of variable physical and biological states within man on susceptibility to, and course of, disease induced by these agents.

LABORATORY RESEARCH

During the fiscal year, the principal scientific support facilities at the National Environmental Health Sciences Center (NEHSC)—the intramural research component of the NIEHS—were fully developed. Liaison with Triangle Universities was further developed, contact on a scientist-to-scientist basis between various Federal agencies was encouraged, and contract support of research projects was increased.

CONTRACTS

Funds were provided for contracts for studies of: mechanisms by which the metals lead, nickel, cadmium, and zinc interact with cellular organelles and affect metabolism; the role of fungi in the production of toxins in cigarette smoke; the effects of toxic chemicals on cell membranes; a method for estimating population exposures to metals of toxicological interest; the effects of inhalation of radon and its daughters upon the induction of bronchogenic carinoma in uranium miners; uranium miner hazards associated with radon, and for establishment of a Beryllium Case Registry.

STAFF RESEARCH

Staff scientists initiated and continued research activity in support of the Institute's mission. This work was administered through the Analytical and Synthetic Chemistry, Animal Science and Technology, Cell Biology, Pathologic Physiology and Pharmacology and Toxicology Branches.

SCIENTIFIC INFORMATION AND COMMUNICATION

Scientific liaison with categorical environmental health programs—particularly with those of the Consumer Protection and Environmental Health Service—has been greatly expanded during fiscal year 1969. Greater emphasis has been placed on lateral communications between responsible individuals at all levels and on participation in ad hoc discussions on topics of mutual concern. Lead, coal workers' pneumoconiosis, beryllium, and asbestos in particular have come under joint consideration; and the uranium miners' problem continues to be the subject of cooperative study. The quick retrieval system for scientific information that was designed in fiscal year 1968 has been extensively used during fiscal year 1969.

Projects initiated by the Scientific Information Office during the year include a review of the spectrum of environmental stressors; identifying the central points of high priority; the preparation of responses to inquiries from other units of Government, and the operation of national registries of clinical cases resulting from exposure to environmental stressors.

OFFICE OF DEMOGRAPHY

Despite intentions to recruit an Associate Director for Demography during fiscal year 1969, constraints in space, budget, and personnel made it advisable to postpone this plan. Recruiting efforts were limited to staffing of two positions in the Biometry Branch in North Carolina and to strengthening of professional and supportive staff of the Occupational Studies Unit of the Epidemiology Branch in Bethesda.

CONSULTATIVE SERVICES

During the past year, the Institute has provided consultative services, guidance, and staff documents to other Federal agencies on a wide range of environmental health problems: hazards associated with high nitrate concentration in foods, particularly baby foods; present status of the beryllium problem; tolerance limits for DDT in milk; organization and preparation of a research program on smoking and health; information for noise abatement program; critical needs of the Nation in environmental health; environmental factors providing competing etiology with smoking in producing cancer of the lungs and other organs, and skin disorders in warm, humid climates.

RESEARCH GRANTS

The Institute in fiscal year 1969 obligated $7.8 million for extramural research projects. Accomplishments in projects that are in the mainstream of the Institute's program interests include:

For example, it has previously been demonstrated that levels of residues in the blood of individuals exposed to the pesticide DDT and other chlorinated hydrocarbons are very low. Estimates of body burden due to cumulative exposure to these pesticides have heretofore depended primarily on analysis of body fat. A group of NIEHS grantees have developed a new and sensitive analytic method for DDT and derivatives that makes it possible to study the relationship between intake (exposure), blood concentrations, and body burden. It now becomes feasible to study large population groups relative to exposure history, as well as to do metabolic studies of these materials in humans in some depth and detail.

Other NIEHS grantees have developed new methods for assessing the effects of pesticides and other chemicals on biochemical mechanisms. The investigators developed assays based on the effects of the pesticides in inhibiting or inducing microsomal detoxification enzymes. This permits the prediction of interactions and obviates the need to test the toxicity of every important combination.

Recently, the importance of potential synergistic activity of mycotoxins and their metabolites or intermediates has been noted. Attention has also been focused upon the fact that the detection, identification, and biological evaluation of toxic substances in food, both untreated and treated with pesticides, will require biological methods that are more feasible than the presently available mammalian systems. Recently, NIEHS grantees have developed a bioassay method using a small crustacean (*Daphnia magna*) that is easy and inexpensive to rear on a purified diet, easy to utilize in numbers up to 100 animals per test, and very sensitive to a wide range of toxic agents. This method has proved to be extremely useful for primary screening of possible toxic situations.

Beryllium is widely used in alloys, as an ingredient in rocket fuels, and, in the past, was used as a phosphor in lamps. Its compounds, dust, and fumes cause a severe granulamatosis disease of the lungs, skin, liver, kidneys, spleen, and lymph nodes; and there is evidence from experimental animals that it is carcinogenic. Little is known about the basic mechanism by which beryllium causes these dramatic biological effects. It has been observed in tissue culture that beryllium concentrates in the nuclei and inhibits mitoses, synthesis of DNA, and synthesis of nucleolar but not nuclear protein. By the use of isotope techniques, these effects have now been confirmed and extended in intact animals.

There is accumulating evidence that exposure to asbestos constitutes a greater risk to health than had been previously recognized. A study now has been completed of insulation workers who were exposed to levels of asbestos fibers in a work environment that for many years had been controlled in accord with good industrial-hygiene practice. Nevertheless, the workers exposed to these supposedly safe levels were found to have excess pulmonary disease in comparison with control workers matched for age and smoking habits.

The significance of these observations relates not only to the danger of developing asbestosis, but to an increased risk of lung cancer and other cancers, inasmuch as increased cancer risk is known to be associated with asbestosis (or other evidence of increased asbestos exposure). This study is being expanded.

A critical problem in trying to evaluate the relationship between lung cancer in uranium miners and their occupational exposure to radioactive gases and dust has been how to evaluate past exposure histories. It is known that exposure to lead-210 or its precursors is closely correlated with exposure to radon and radon daughters and that lead-210 is deposited in the skeletal system and is very slowly lost from the body. Therefore, a reliable and practical method of measuring body burden of lead-210 should provide an accumulative history of exposure. NIEHS grantees have recently developed and tested a new whole-body counter that is capable of measuring the X-rays emitted by lead-210, with minimum interference from other radioactive elements usually present.

Toluene diisocynate (TDI) is a chemical in the plastics industry to which thousands of workers are regularly exposed. A detailed study by NIEHS grantees of 38 workers in a polyethylene-foam factory indicated that although industrial-hygiene practices were good and air concentrations of TDI were within a safe range both acute and chronic decrements of respiratory function were significantly above normal.

RESEARCH TRAINING

The Institute made its first research career development awards during fiscal year 1969. Through a reprograming of funds, it was possible to make five awards.

UNIVERSITY-BASED CENTERS

A key development for this segment of the extramural program was the appointment of a standing subcommittee on university-based centers, as an offspring of the Environmental Health Sciences Advisory Committee. This subcommittee has served a two-fold role: providing a forum for discussion on administrative matters associated with individual center programs, and engaging in studies of policy issues relating to program development, site selection and interrelationships of centers.

Members of the subcommittee participated actively in preliminary steps that led to administrative conversion of the project at Vanderbilt

Table 1.—***National Institute of Environmental Health Sciences, distribution of appropriation***

[In thousands]

	1968 actual	1969 estimate
Research grants:		
Regular program:		
Noncompeting	$3,631	$3,572
Competing	360	369
Supplemental	34	
New	924	1,154
Total, regular	4,949	5,095
Special program:		
General research support	547	551
University-based centers	3,000	2,993
Total, special	3,547	3,544
Total, research grants	8,496	8,639
Fellowships	42	193
Training grants	3,763	3,650
Total, grants	12,301	12,482
Laboratory and clinical research	2,825	2,968
Research contracts	(583)	(653)
Review and Approval	302	294
Program direction	274	300
Management fund	1,006	1,201
Total, direct operations	4,407	5,416
Total	16,708	17,898

University to the status of center. This action did not result in a net increase in numbers of centers, owing to the termination of a grant for a pilot-center program at Purdue University.

Table 2.—*National Institute of Environmental Health Sciences research grants program analysis*

	1969 Estimate
Toxicology	$2,376,000
Pesticides	1,748,000
Natural products	388,000
Synthetic organics	204,000
Heavy metals	182,000
Smoking and health	100,000
Alpha emitters	97,000
Subtotal, regular program	5,095,000
General research support grants	551,000
University-based centers	2,993,000
Total, research grants	8,639,000

National Institute of General Medical Sciences

The National Institute of General Medical Sciences supports research and training in the sciences basic to medicine and in certain clinical disciplines central to the Nation's total health effort. It provides core support of medical education through the production of faculty for medical schools.

The Institute selectively supports various combinations of basic and applied research to meet acute and urgent needs.

It gives highest priority to three programs to discover and develop: (1) new knowledge crucial to safer and more effective use of drugs; (2) faster, more reliable and less costly methods for the prevention and diagnosis of disease, (3) improved ways to care for injured patients.

PHARMACOLOGY-TOXICOLOGY

The Institute's program in pharmacology and toxicology has been developed with funds appropriated by Congress to solve problems arising from society's increasing reliance upon drugs and medications. These funds, totaling $3.5 million for each of the past 3 years, have enabled the Institute to help establish and support several university-based centers of drug research and initiate a number of smaller contract projects. The program this past year produced findings of direct and immediate benefit to patients.

In one project, for example, it was determined conclusively that women with type A blood who use birth-control pills are significantly more likely to develop thromboembolic disease or clotting problems than women with type O blood. As a result, physicians are now better able to counsel women concerning the use of oral contraceptives. Meanwhile, basic scientists have undertaken a study to learn which of the complex proteins involved in clotting are different in type O and type A patients. They hope to find ways of preventing abnormal clotting in patients with heart attacks and stroke, where similar problems are involved. It was also learned that a new, highly potent diuretic drug, commercially available for less than two years, may cause severe gastrointestinal bleeding, especially when administered by injection.

Another team of investigators clearly showed that a group of antidepressants, or tranquilizer drugs, drastically interfere with the antihypertensive action of guanethidine and related drugs. Their discovery is extremely important, as guanethidine is widely used in the treatment of high blood pressure, and because the concurrent use of tranquilizers is on the increase. Each of these studies is part of a program of drug surveillance to identify causes of adverse drug reactions and discover ways for their prevention.

Other investigators found that a commonly used central nervous system stimulant, methylphenidate (Ritalin), inhibits normal metabolic excretion of anticonvulsant agents administered to children with epilepsy. In this type of drug-drug interaction, the blood level of one anticonvulsant agent, dephenylhydantoin (Dilantin) was raised to a toxic level, sufficient to produce ataxia. In related studies it was shown that methylphenidate likewise interferes with the normal metabolism of various anticoagulant agents, leading to increased plasma concentrations and hemorrhage.

Several investigators have developed and are using in clinical studies exquisitely sensitive instruments linked to computers which rapidly and accurately measure trace quantities of drugs and their metabolites in extremely small quantities of biological fluids, such as urine and blood. These methods are now being used to study drug concentrations in newborn infants; this was previously not possible because of the much larger samples required for traditional assays.

In this study, traces of aspirin, tranquilizers, alcohol, and other chemical residues have been found in many infants, showing further that the so-called "placental barrier," is a myth, at least pharmacologically, and that women should be cautious in their use of drugs and chemicals during pregnancy. The investigators observed a symptom complex lasting as long as 9 months in babies whose mothers were receiving tranquilizers.

AUTOMATION OF CLINICAL LABORATORIES

Automation in clinical laboratories must be developed to speed and improve diagnosis, and to detect disease in the earliest stages when it is most amenable to treatment, less hazardous and less costly to deal with.

To this end, the Institute is developing a balanced and integrated program of basic and applied research designed to automate routine analytical procedures common to all hospital laboratories.

Applied research, best accomplished through contract support, is necessary to exploit new technologies for automated, flow-through analytical systems. Existing technologies, proven in basic laboratories but not yet fully utilized in clinical testing, include ultraviolet and infrared spectrophotometry, gas chromatography, mass spectroscopy, and centrifugation. These techniques are far more sensitive and accurate than existing visual colorimetric methods, which have been laboratory mainstays for over 50 years.

The Institute's funds for collaborative or contracted research and development in the automation program during 1969 were limited to less than $1 million. Nevertheless, as a result of the Institute's collaborative project at the Atomic Energy Commission's Oak Ridge National Laboratory, three highly significant developments may be noted.

One is of a revolutionary analytical system employing a new mixing technique which can determine the concentration of sugar in 50 different patients within a 2-minute period. Thus far methods have been developed for the analysis of 10 different constituents of blood. The test data are recorded photographically, calculated by computer, and printed out for use by the physician within minutes after his request. Prototypes of this instrument are now being produced by three companies for field testing.

A second is the development of a computerized instrument system which reliably detects up to 140 different ultraviolet absorbing constituents in urine, more than four times the number detected by conventional urinalysis. Several protoypes are now being evaluated in university hospital laboratories. Many of the "fingerprint" peaks produced by this system of urinalysis have been found to be of medical significance and in fact appear to present distinct "profiles" for several disease entities.

Another promising achievement is the development and fabrication of a high-resolution prototype analyzer which rapidly separates carbohydrate fractions from samples of body fluids, including intermediate products of carbohydrate metabolism and sugar molecules.

Up to 50 different sugars have been identified in a single sample of urine. The developers believe the unit will be of great value in detection of diabetes and other carbohydrate diseases.

Institute-supported investigators are attacking problems associated with the separation and identification of enzymes. One has developed a computer-instrument system to provide digital readouts of enzyme activity. Another group has devised detectors for analyzing metabolic products, including fatty acids, aldehydes, amines, and alcohols.

They have found that the concentration of circulating free-fatty acids in adults varies in response to surgical stress. This work recently was extended to study catecholamines in infants, to clarify their responses to stress.

TRAUMA

National Safety Council reports for 1968 show that accidental injuries—or trauma—took the lives of 114,000 people in the United States and were the leading cause of death in the 1–44 year age group. More than 10 million injured persons were temporarily disabled and another 400,000 were permanently impaired. The cost of accidental injuries, including hospitalization charges and lost wages, was said to be $22.5 billion.

For several years the Institute has sought to develop an effective progam to speed discovery and application of new methods for treating injured persons. In many cases of fatal injury, death is not outright but comes hours or days later from occult and little understood causes—acute liver or kidney failure for example—which present a sydrome much like that of patients seriously ill from other causes. Solving urgent problems of trauma thus will benefit not just the injured but other critcally ill patients.

The Institute has developed special centers where scientists may study multiple aspects of trauma, using both basic and clinical techniques to obtain maximum data from injured patients, who characteristically are difficult to study.

Although funds for new projects were extremely scarce in 1969, the Institute was able to initiate one new trauma center by lessening support for investigations in other important but not as crucial fields. This brought to seven the number supported during the year at a total cost of $1.4 million. In general, while the Institute's program still is relatively new, it has become increasingly productive.

For example, the discovery in one study that cells consume oxygen more readily in early stages of tissue repair led the investigators to develop a technique which appears to speed the healing of wounds. This was achieved in a number of injured patients by surrounding their wounds with a pressurized plastic bag containing humified oxygen.

Another significant finding is that vitamin A applied topically to open wounds markedly overcomes the retardation of healing caused by steroid drugs notably cortisone. Because cortisone acts to inhibit inflammation, it helps millions of patients having rheumatic fever, arthritis, gout, and other inflammatory diseases. Inflammation, though, is needed to trigger the body's natural healing processes following injury. Open wounds in patients receiving cortisone therefore tend to heal poorly and the risk of infection is greater. The discovery with vitamin A may thus have solved a serious and widespread problem in surgery.

Investigation of metabolic rates has revealed significant differences between trauma patients and those subjected to the stress of surgery. The resting rate of metabolism among patients following elective, uncomplicated major surgery was found to be unchanged from preoperative levels, while patients with multiple fractures, peritonitis and severe burns demonstrated higher levels. This knowledge bears importantly upon nutritional aspects of care for badly injured persons.

A new antibacterial ointment synthesized with Institute support has proved highly effective in treating burn wounds among patients in several hospitals. It particularly has been useful in stemming infections from the common bacterium, *Pseudomonas aeruginosa*, that become severe when protective body mechanisms are weakened by burn wounds. Tests also demonstrated that some burns treated with the compound healed well without concurrent administration of supplementary fluids. In several cases, areas of partly destroyed skin were saved and skin grafting was not required. The importance of this development is seen in the fact that burn injuries, complicated by infection and fluid loss, are extremely difficult to treat and lead to death for some 10,000 persons each year.

FUNDAMENTAL SCIENCES

The Institute's fundamental or general research program supports a large number of diverse approaches to very broad problems in biomedicine. These depend greatly upon the inventive minds of single investigators, for which the individual small grant is vital.

Broadly speaking, the program seeks to achieve greater understanding of the structure and functions of the human body, and of ways in which life processes become altered by disease and injury. Of special interest are studies of the physical and chemical properties of cells, and of their interrelationships and functions as parts of tissues and complex body systems. Many studies are in genetics, and seek to learn how organisms reproduce, how abnormalities occur in the process, and how these can be prevented or corrected.

Findings from these investigations contribute directly and importantly to the Institute's special or targeted programs. They serve to expand the common core of knowledge of health and disease. In this way, they reinforce advances in other research units of the NIH.

For example, a biophysicist supported by the Institute recently discovered an entirely new class of anticancer agents—platinum compounds—which in mice potently inhibit tumors and produce striking remissions of leukemia, seemingly without harm. This is the first time inorganic substances have been found to exhibit such properties. His discovery is now being extended by the National Cancer Institute to test further the anti-leukemia activity of the agents and their potential for use against cancer in man.

An Institute-supported scientist found a simple way to treat blood samples chemically to determine if individuals have a genetic abnormality that makes them deficient in the enzyme pseudocholinesterase. The discovery is of significance in surgery, because patients who lack the enzyme cannot metabolize a potent muscle relaxing drug, succinylcholine chloride, which often is used in conjunction with anesthesia during operations. The drug therefore can be toxic to such patients and occasionally has led to death. Of some 25 million Americans who undergo surgery each year, it is believed that one in 3,000 is pseudocholinesterase deficient. The finding also has implications in Institute programs in pharmacology and toxicology, medical laboratory chemistry and anesthesiology.

As a result of another investigation in genetics, twin boys, from the moment of their birth, have been receiving chemical treatment, the first of its kind, to lessen the effects of a rare sex-linked disease. The disorder, known as Lesch-Nyhan disease, affects only male offspring. It is characterized by an inborn error in purine metabolism and is very damaging neurologically. That these boys would have the disease was learned, beyond question, early in the mother's pregnancy.

By examining embryonic cells taken from the mother in her 21st week of pregnancy, it was determined that the fetus (the existence of twins was not disclosed at the time) would be male. It also was found that the cells were mutant and deficient in purine metabolism, and failed to grow unless the culture medium was supplemented with adenine or high levels of folic acid. These chemicals appeared to overcome the cellular defect.

Therapy with both adenine and folic acid thus was commenced immediately upon birth of the twins. After 7 months, the grantee investigators reported very encouraging results, but it will take several years to evaluate fully the effectiveness of treatment. Meanwhile, this two-step achievement in diagnosis and therapy is of tremendous significance, since the techniques involved may be applicable to other kinds of inherited anomalies. The study also demonstrates how new basic knowledge can be applied rapidly to treat and prevent genetic diseases.

RESEARCH TRAINING

In universities and medical schools throughout the country, the Institute during this year supported some 600 biomedical research training programs which produce many of the scientists necessary to assure the future advancement of medicine and health care. There were some 5,000 predoctoral and 1,000 postdoctoral trainees in these programs. Advanced training was provided for another 2,400 promising young men and women through research fellowship awards.

A group from the National Academy of Sciences has been engaged since November 1965 in a study contracted for by the Institute to assess the impact of its training programs on the number and quality of bioscientists being produced, and on the departments and institutions which produced them. By the end of the fiscal year (June 1969) the study was virtually completed and preparations were being made for the data to be published.

Preliminary findings of key interest may be summarized as follows:

- In general, departments receiving Institute training support produced substantially more than the average number of Ph. D.'s in their fields; they have grown more rapidly in terms both of doctoral output and graduate enrollment, they have shown much larger increases in their professional staff to improve the quality of training.
- The number of doctoral degrees earned in fields supported by Institute training grants has increased more rapidly than in bioscience fields it does not support.
- Bioscience trainees who received Institute support required 1 to 2 years less time to obtain the Ph. D. than those who did not.
- As a measure of quality, Institute trained Ph. D.'s—compared to a randomly selected group of nonsupported bioscience Ph. D.'s—published their work altogether more and more often, and their work was cited altogether more and more often than the nonsupported group.

In effect, the study data show clearly that with Government support administered by the Institute more people are being trained better and faster than when there is no Government support.

It may be noted, too, that a large portion of Institute trainees are recruited to faculty positions in the Nation's medical schools. Its training programs thus constitute a vital, core resource for the production of physicians who are badly needed in much greater numbers to provide health services to people who need care.

To coincide with school enrollment periods, Institute training programs are administered under a so-called "forward finance" procedure. That is, training support in 1969 was derived from the Institute's appropriation for 1968. By the same token, the level of training support in fiscal year 1970 is based on the fiscal year 1969 appropriation.

Accordingly, 22 fewer training programs are being supported from the Institute's 1969 appropriation, than in 1968. Interestingly enough, training funds made available in fiscal year 1969 were increased $2.4 million over the amount appropriated in 1968. It thus would have seemed likely that the number of programs would go up rather than down. That is not the case, though, and reductions were required because the appropriation increase amounted to 5 percent, while stipends, tuition charges, and other built-in costs of training increased at a rate of about 8 percent.

National Institute of Neurological Diseases and Stroke

More than 200 clinical disabilities are associated with dysfunction, disease, or injury of the nervous system. The National Institute of Neurological Diseases and Stroke has the main responsibility for research on the cause and treatment of these conditions.

Among the most urgent of the Institute's problems is the need for a safe and effective method to diagnose impending strokes, immediate and effective treatment for brain and spinal cord injury, and more effective drugs for epilepsy. A large research effort is also being applied to the problems of multiple sclerosis, cerebral palsy, muscular dystrophy, and deafness.

Since its creation in 1950, the NINDS has developed a broad program of basic and applied research. During the past year, several changes were made. First, the Institute's blindness program was incorporated into the new National Eye Institute, signed into law by President Johnson on August 17, 1968. Later, the name of the parent organization was changed to the National Institute of Neurological Diseases and Stroke to reflect the Institute's responsibility in cerebrovascular research.

During the year an expanded intramural research program was made possible by the addition of a new laboratory building, equipped with the most modern facilities. The new facility and the addition of four new laboratories to the existing eight have made it possible to open up research in additional areas. Research was stepped up in such basic areas as neuroanatomy, and in specialized studies such as the response of the central nervous system to physiological and noxious stimuli. The new Laboratory of Neural Control is working on the problem of harnessing nervous energy to operate prosthetic devices.

COLLABORATIVE PERINATAL PROJECT

Recent findings in the Institute's giant mother-child study may lead to the prevention of many neurological deficits which have their source during the perinatal period (around the time of birth). For example, a new screening test, based on high immunoglobulin levels in cord blood, has been developed for detecting infections in newborn infants. Since an elevated IgM level indicates that some sort of disease process is going on, the test may serve as a valuable index for alerting physicians to infection in babies less than 3 months old.

A major cause of birth defects in children, rubella, is being brought under control, partly as a result of NINDS efforts. A vaccine program now under way is expected to eliminate this serious threat to the developing fetus. NINDS has accumulated further evidence that rubella infections during the second trimester, as well as the first, also affect the fetus.

Congenital infection of the child, when the mother was infected with German measles in the second trimester, has been proven in a number of instances through serological determinations and virus isolation from the youngster. Also certain defects including growth retardation and hearing loss have been observed in some children.

Severe and prolonged hypoglycemia in childhood (a condition of low blood sugar levels) has been further confirmed as a cause of cerebral palsy and mental retardation. Treatment methods, consisting of a special diet with feedings every 3 hours, have been worked out for exceptionally severe cases of hypoglycemia of unknown cause. Studies of hypoglycemic children who are sensitive to the amino acid leucine, found in most proteins, have shown that this variety of the disease often improves spontaneously from 3 to 6 years of age. This finding makes it possible for physicians to counsel families in which the disease tends to occur and demonstrates that if hypoglycemia can be controlled during infancy, permanent brain damage can be prevented in this not uncommon disease.

Toxoplasmosis, a disease which can cause severe neurological damage to the developing fetus, has long been a puzzle to medical science because its mode of transmission remained a mystery. NINDS investigators have now detected a human-borne parasite whose presence is closely associated with evidence of exposure to the infection in Puerto Rican children. Estimates indicate that of the congenital toxoplasmosis cases which survive, 85 percent are mentally retarded and more than 70 percent are spastic. Once the disease carrier is pinned down, work can begin on development of preventive treatment.

EPILEPSY

Another condition arising in childhood is epilepsy. From its beginning, the Institute has allocated a large share of its research effort to this malady. One study in children has shown that a high fat diet can lead to better control of seizures than has been possible with anticonvulsants. Another effort has been made to research methods for treating patients with intractable epilepsy who are unresponsive to anticonvulsant drugs and not within reach of surgery. It was found that many of these uncontrolled seizures can be treated effectively medically after local brain cooling, which allows drugs to cross the blood brain barrier.

One of the most tragic aspects of epilepsy is that, even today, the ancient social stigma toward its victims still lingers. To counteract this, the NINDS Information Office and the National Epilepsy Foundation are mapping a national educational program. In addition to informing people, it will attempt to encourage those with epilepsy to use all known methods of therapy, and will encourage educational and work opportunities for all those able to participate.

DISORDERS OF THE AGED

Several neurological disorders mainly affect the aged. Of these, stroke (cerebrovascular disease) is one of the three great cripplers and killers—heart, cancer, and stroke. NINDS and the National Heart Institute support a number of stroke research centers in major universities and hospitals. Several centers concentrate on a single problem area, such as aphasia (speech disorders) or epidemiology (community statistics). Other centers undertake several approaches, such as the events surrounding a stroke (its natural history), study of blood flow through vessels, the effect of anticonvulsant drugs, and the use of food materials by the brain (cerebral cellular metabolism).

Epidemiological studies of stroke are important because they provide clues to its causes, and possible means of prevention. For example, accumulated data have suggested striking differences in the occurrence of death due to stroke in different parts of the United States. In late 1968, the difference was definitely verified. A nine-city epedmiological project funded by NINDS showed a measurably higher rate among white males in the deep South than in other parts of the country.

In another degenerative condition of older people, Parkinson's disease, several hundred patients have found relief through the use of two experimental drugs. One drug, L-DOPA, last year was found beneficial to 75 percent of patients in NINDS-supported drug trials. Field trials of L-DOPA are now being conducted to satisfy the requirements of the Food and Drug Administration for safety and effectiveness. It is hoped that this enzyme inhibiting drug, or similar drugs, after the necessary refinements, will become widely available in the coming months.

Another drug, amantadine hydrochloride, was first used as an antiviral agent for Asian influenza. In one trial of this drug on 163 Parkinson's disease patients, 107 showed some improvement.

SCLEROSING DISORDERS

Among the most tragic of all diseases are the sclerosing disorders which strike their victims in the prime of life. Institute conducted and supported research on the most common of these disorders, multiple sclerosis, has discovered clues which may soon reveal the cause.

Several clues now point to the possibility that MS (as well as parkinsonism and a number of other neurological diseases) may be of viral origin. In addition to the previously announced discovery that kuru is a virus disease, a more prevalent disease, Jakob-Creutzfeldt's, has now been successfully transmitted to chimpanzees.

In further support of the virus theory, Institute scientists recently identified measles virus in biopsy material from patients with subacute sclerosing panencephalitis (SSPE). The virus was identified through a new tissue culture technique. This is now being applied to biopsy specimens of patients with MS and other neurological diseases for which there is indirect suggestive evidence that a virus may be implicated.

NEUROMUSCULAR DISEASES

The neuromuscular diseases primarily affect America's greatest assets—her children and young adults. The two most prevalent neuromuscular ailments are muscular dystrophy (MD) and myasthenia gravis, the former affecting mostly children and the latter young adults.

Knowledge of the fundamental mechanism in muscular dystrophy is progressing rapidly. For example, researchers may soon be able to identify women who carry the gene for the X-linked disorder Duchenne dystrophy, by chemical tests and muscle biopsy. Clinically normal carriers of the disease have atrophy and architectural derangement of scattered or slightly grouped muscle fibers. Identification of carriers is essential for genetic counselling.

Enzymatic and biochemical studies of NINDS grantees showed that phosphofructokinase (PFK) and myoglobin were missing from the serum of Duchenne dystrophy patients and that phosphorylase (PPL) activity was abnormally low. This finding is important to the goal of elucidating the fundamental defect in this disorder.

Several neuromuscular diseases are caused by inborn errors of metabolism. More knowledge has recently been gained about two of these diseases. Metachromatic leucodystrophy (MLD), a progressive degenerative neurological disease characterized by a defective enzyme, can now be specifically diagnosed by a blood test developed by NINDS scientists. The metabolism of the ganglioside which accumulates in the neurons of patients with Tay-Sachs disease has been successfully demonstrated for the first time. The investigators have synthesized this ganglioside, whose accumulation produces the symptoms of the disorder, and have labelled it radioactively to study the specific abnormal enzymatic reactions which produce the metabolic defect.

HEAD INJURY RESEARCH

Brain and spinal chord injury too often dooms the victim and overwhelms his family. Brain damage may cause death or prolonged coma or may leave persistent mental confusion. Spinal cord damage often causes severe paralysis. To solve these problems, the Institute has launched a pilot program of multidisciplinary centers for clinical research on head and spinal cord injury.

In research related to the spinal cord and central nervous system, whiplash as well as direct impact injury has been found to produce brain concussion and hemorrhage. A new electronic technique has practically eliminated spinal cord surgery for pain relief.

DISORDERS OF COMMUNICATION

An estimated 20 million people in this country have one or more communicative disorders. Such disorders include deafness, late speech acquisition or failure to talk, defects of articulation, and inability to receive, interpret, retain, and express language, including aphasia and central disorders of perception.

As a first priority in mounting an attack on this massive problem, the NINDS has placed major emphasis on training. Currently, 389 post-doctoral students are studying with Institute support through 78 grants to institutions for advanced research training in otolaryngology, audiology, sensory physiology, and related disciplines.

Other activities in the human communications field conducted or supported by the NINDS include 174 separate research projects at 82 medical centers, five multidisciplinary clinical research centers, and three out-patient clinics. The Institute supports four temporal bone banks for the long-term study of structural and pathological changes relating to functional disorders of hearing. It recently established an information center for hearing, speech, and disorders of communication. The Institute published three monographs to provide physicians, educators, and therapists new information relating to communicative disorders.

Clinical Center

The Clinical Center is a 516-bed research hospital which provides the necessary facilities and support services for the clinical investigation programs of the several NIH Institutes with clinical research activities.

The Clinical Center was originally designed by Dr. Jack Masur, who served as Director of the Clinical Center from 1948 to 1951 and again from November 1, 1956, until his death in March of 1969. Under Dr. Masur's direction, the Clinical Center evolved the highest standards for evaluating every decision affecting a patient so that the welfare of the patient takes precedence over other considerations; this assures that each patient receives the finest care and treatment possible while participating in one of the research protocols.

During fiscal year 1969, 4,021 patients were admitted to the Clinical Center. Of these, 1,225 inpatients were admitted for the first time. By the nature of the research done by the several Institutes, the Clinical Center is a chronic disease hospital. As a result, the average length of stay was 31 days and the bed occupancy rate averaged 65 percent.

One of the last alterations approved by the late Dr. Masur, which was completed this year, was an addition of 110,000 square feet of floor space making its total now over 1,360,000 square feet. This additional space will make patient care facilities available to the National Institute of Child Health and Human Development. This will be the eighth Institute to use the complete and sophisticated services of the Clinical Center.

Division of Biologics Standards

The Division of Biologics Standards (DBS) is responsible for administration of those provisions of the Public Health Service Act concerned with the Federal licensing and control of biologic products that are offered for sale in interstate commerce or for export or import.

These include vaccines, serums, toxins, antitoxins, as well as human blood and its derivatives, that are used for the prevention and treatment of diseases in man.

HONG KONG INFLUENZA

Influenza vaccine, because of the changing character of the virus, presents problems in biologics control almost every year. During the fall of 1968 it became a matter of unusual concern because of the emergence in the Fast East of a highly divergent A_2 strain. In late June, an increase in respiratory illness was noted in Hong Kong. Isolation of viruses was made in Hong Kong and cultures were transmitted to laboratories in different parts of the world for study. By August 13, there was agreement among the virologists that these cultures differed markedly from A_2 strains prevalent in recent years. The change was so marked that the ultimate development of an epidemic was clearly predictable, since available vaccines could be expected to provide no more than limited protection.

Knowing that the normal leadtime for production of influenza vaccine is 4 to 5 months, the DBS immediately provided cultures of this Hong Kong variant to the vaccine manufacturers so that they could study its properties and determine whether a vaccine could be produced from it. Manipulation of influenza virus preparatory to vaccine production is sometimes a lengthy and troublesome process, since a new strain must be adapted to growth in fertile hens' eggs through an unpredictable number of generations or "passages." While this work was in progress, a new isolate of the virus was received from the Far East which clearly had a superior vaccine production potential. This strain was provided to the manufacturers on September 9 by the DBS. Testing methods and procedures were worked out by DBS and correlated in numerous conferences and laboratory demonstrations with the manufacturers. To expedite the processing and release of vaccine, concurrent testing of vaccine lots was carried out by the DBS and the manufacturers. This required an intensive commitment of DBS resources to testing and review procedures prior to release of vaccine lots.

When the first experimental lots became available, the DBS was able to embark on clinical evaluation of the vaccine. The Division diverted a portion of its early Hong Kong vaccine which was reserved for control purposes to volunteer studies which can best be performed during an epidemic situation. The vaccine was made available by the DBS to the NIAID Vaccine Development Branch, and to other investigators. Several of these teams are working in close collaboration with the DBS Laboratory of Virology and Rickettsiology. Because of the nature of these studies, however, it will be several months before the results are known.

The first lot of Hong Kong influenza vaccine, containing 110,000 doses was released on November 15, 1968. In the ensuing weeks, additional lots were produced and released, to provide a total of 20,934,645 doses.

RUBELLA VACCINE

The DBS team which produced the first effective experimental rubella vaccine from their attenuated strain (HPV–77) continued its research activities. The work expanded as large stocks of HPV–77-strain experimental vaccines produced by pharmaceutical manufacturers became available. As of June 1, approximately 45,000 persons had been inoculated with HPV–77 or HPV–77-derivative vaccines. None of the inoculated experienced adverse reactions to the vaccine, and approximately 98 percent developed antibodies indicative of immunity. Equally important, the vaccine virus has not spread to any of the thousands of carefully studied contacts of vaccinees.

Pharmaceutical groups have produced HPV–77 experimental vaccines in duck embryo, dog kidney, and monkey kidney tissue cultures. All have been used to prepare vaccines for field trials in the United States, Canada, England, France, Russia, Holland, Finland, Sweden, and Taiwan. In 1967, the DBS team succeeded in adapting the virus to chick embryo tissue cultures and produced an experimental avianized rubella vaccine. However, the results of clinical trials, completed in the spring of 1968, indicated that propagation of the virus in chick cells resulted in "overattenuation." Only 75 percent of children given the vaccine developed anibodies. Recently, additional derivatives of HPV–77 were adapted to chick embryo by the DBS team and this new series of experimental vaccine is currently on clinical trial.

The DBS team supervised ten rubella vaccine trials to provide information relating to the potential usefulness and safety of the vaccine. In one study, the effectiveness of the vaccine given by injection and intranasally was compared. In another, the vaccine was shown to be 100 percent protective in vaccinated children challenged 1 year later with natural rubella virus. Highly modified attenuated strains developed in DBS and elsewhere were tested in volunteers in comparison with HPV–77 to determine the options available in selection of ideal attenuated strains. These studies showed that the more highly modified viruses were less desirable.

The duration of vaccine-induced immunity is particularly important. Recent tests three full years after immunization of the first groups of girls in the pilot study at the Children's Colony, Conway, Ark., indicate that the level of vaccine-induced protective antibodies in their blood is unchanged. This indicates that the immunity is likely to be long-lasting.

Vaccine studies have been expanded to include diverse, special-interest groups: nursing mothers, children with chronic diseases, and representatives of age groups for which immunization is intended. The HI blood test for rubella immunity, developed by the DBS team in 1966, has become commercially available and is reaching full application in laboratories and hospitals throughout the country. Its use has been invaluable in accelerating the vaccine development program. The test identifies persons susceptible to rubella as candidates for immunization. After inoculation, a second test is made to measure the effectiveness of the vaccine.

It is estimated that the HI test advanced the target date of a final rubella vaccine by nearly a year, and has resulted in a saving of over a million dollars in government expenditures for rubella vaccine research.

Administrative steps that must precede the licensing of a new biological have been taken by the DBS. These include standardization and distribution of official reference preparations of the vaccine, and development of additional standards pertaining to its manufacture.

On June 10, 1969, the Secretary, DHEW, announced the licensing of the first rubella vaccine for commercial use in this country.

Additional vaccines currently under consideration are expected to be licensed as testing and evaluation programs are completed.

TUBERCULIN

Most of the tuberculin sensitivity in the United States is due to infection with organisms related to but different from those that cause tuberculosis. It is important, from the standpoint of treatment, to be able to determine whether a person who converts from a tuberculin negative to a tuberculin positive status is infected with the tubercle bacillus or one of its relatives. The DBS Laboratory of Bacterial Products has been carrying on research to help resolve this problem. To determine which organisms are most likely to be responsible for tuberculin reactivity, white blood cells from the venous circulation are cultured in the presence of antigens prepared from the tubercle bacillus and related organisms. Antigenic material from the organism that is infecting the individual usually stimulates the white cells to metabolize at a faster rate than antigenic material from other organisms. This is detected by the incorporation of isotopically labeled precursors into the stimulated cells.

The *in vitro* test correlates well with skin reactivity in sensitive human beings and animals. With skin testing, the number of antigens that can be introduced into an individual is limited since reactions may be very severe if the concentrations are not carefully selected. Often suppression of reactions may be seen if too many reagents are used or in too concentrated a form. The *in vitro* test permits a battery of antigens at different concentrations to be tested in the sensitive individual. The constituents present in extracts of the various mycobacterial organisms are being analyzed. It is hoped specific skin-reactive substances characteristic of each type of organism can be prepared. Such substances would be of great epidemiologic and diagnostic value.

MYCOPLASMA

Evidence of the implication of *Mycoplasma* in various human diseases has occurred with increasing frequency since these little-understood microorganisms have been studied by sophisticated laboratory and electron microscope techniques. These smallest of all free-living organisms, once called PPLO (pleuropneumonia-like organisms), were first identified more than 60 years ago as the cause of pleuropneumonia in cattle. In 1962 they were found to be the etiological agents of a human disease—primary atypical pneumonia. More recently, they have been studied as to their possible role in the pathogenesis of tumors in man.

It has been known for more than 10 years that tissue cultures harbor *Mycoplasma* as contaminants. The detection, isolation, and identification of these organisms by the DBS Laboratory of Bacterial Products, has resulted in greatly improved cell culture media and the introduction of test procedures to ensure the exclusion of *Mycoplasma* from all vaccines.

The DBS has also arranged for the preparation of relatively large quantities of antiserum against all known *Mycoplasma* species. These reagents will facilitate rapid and accurate identification of these organisms isolated from tissue of patients with diseases of unknown cause, and help establish the role, if any, that they play. The antiserums are also helpful in the identification of *Mycoplasma* recovered in the testing of biologic products.

STUDY OF BLOOD FRACTIONS

Many blood products, such as albumin and globulin, are obtained by fractionating human blood plasma. These plasma proteins, widely used in treatment of injuries and prevention of disease, may be obtained from venous blood or from the human placenta. Recovery of placental plasma involves procedures which may extract tissue components not found in venous plasma. Some researchers have found that albumin obtained from the placenta had a shock-producing activity in experimental animals, but albumin from venous sources did not.

As a result of these findings, the Division's Laboratory of Blood and Blood Products has initiated immunologic studies to determine the number and types of components in albumin and globulin preparations and their biological activities.

Eventually, it may be possible to determine by animal tests which of the components in the placental plasma proteins produce adverse physiologic effects.

YELLOW FEVER VACCINE

Yellow fever vaccine has been licensed for many years and its effectiveness in inducing solid immunity to "wild" yellow fever virus is undisputed. However, the vaccine, which is produced in chick embryos, was developed in the early 1940's when little was known about avian viruses in hens' eggs. Today it is known that many chick embryos may be infected with avian leukosis viruses. During the 25 years that yellow fever vaccine has been in use, there has been no observation of any relation between the avian viruses and human disease; nevertheless, DBS scientists have been working to purify yellow fever seed virus from which the vaccine is prepared without altering the efficacy of the vaccine as an immunizing substance.

Using a unique procedure of differential filtration through membranes of different pore sizes, they succeeded in separating the smaller yellow fever virus from the larger contaminating avian leukosis virus. Laboratory studies were then conducted to ensure that the purification process did not alter the characteristics of the vaccine virus strain. Primary and secondary vaccine seeds of the uncontaminated vaccine have passed the required tests for safety and potency in the laboratory. Following completion of volunteer studies currently under way, the purified yellow fever vaccine seed will be recommended for use in commercial production of yellow fever vaccine.

Division of Computer Research and Technology

The Division of Computer Research and Technology's mission is a dual one: providing the essential services of a central computing facility for the NIH, and simultaneously conducting a broad research effort to apply mathematics, engineering and the computer sciences to support biomedical research.

Significant advancements were made during fiscal year 1969 in modifying the OS/360 central computer facility to serve its 700 users.

PROGRAM ACHIEVEMENTS

During the year the Computer Systems Laboratory (CSL) assisted in the implementation of systems for support of scientists in the laboratories of NIDR, NIAMD, NHI, and NCI. In these, the computers are in a closed loop, monitoring and controlling experiments and simultaneously capturing and analyzing experimental data. The technology provides rapid retrieval of information, from remote locations, on such matters as fluid, colloid and saline solution replacement doses for burns of children; differential diagnosis of diseases of calcium and phosphorus metabolism, and incompatability of intravenously administered drugs.

Continuous electrocardiogram arrhythmia monitoring of intensive-care patients in the NIH Clinical Center was initiated. Existing algorithms were improved and extended to permit analysis of blood pressures and phonocardiograms.

The Laboratory of Applied Studies (LAS) undertook many cooperative projects. The efficiency of different types of artificial heart valves was described mathematically for the National Heart Institute, and electrocardiograms were automatically analyzed as a screening procedure for detecting early heart disease.

Automatic deductive question-answering was investigated by the Heuristics Laboratory. The PDP 10/50 computer was programed to select facts from a humanly unmanageable volume of material and apply them logically to solve problems, for example, of human vision.

Programs permitting quantitative description of the metabolism of radioactively labeled glucose, fatty acids and mineral elements were developed by the Data Management Branch (DMB). Long-term studies were carried out by DMB on the incidence and contributing causes of birth injury and mental retardation, the effects of the work area on diseases among steel workers, and long-term cancer survival studies.

The DCRT continued its series of training courses taught by DCRT employees and made available to computer users without charge. In the spring 1969 term, 29 such courses were given.

Division of Research Grants

The Division of Research Grants assigns applications within NIH to initial review groups and Institutes and Divisions; provides for the scientific review of applications by NIH study sections and review committees; conducts negotiations with grantee institutions and provides advisory and consultative services relative to grant policy and management matters, and collects, stores, retrieves, and analyzes management and program data needed by NIH in the management of its extramural programs.

During fiscal year 1969, the Division initiated and held a series of four experimental conferences designed to provide useful information to NIH science administrators in the allocation of research funds to specific fields of research.

Noteworthy savings in time and money will be effected by the Division's development of new systems designs and techniques for storage, retrieval, and preparation of statistical data for publication. Important among these is the use now made of the Linotron phototypesetting system operated by the Government Printing Office, which will have a marked effect on the timelag between the end of each fiscal year and the availability of grant and award listings.

A committee established by the Assistant Secretary for Health and Scientific Affairs to revise the Public Health Service policy for the protection of individuals as research subjects was chaired by the Director, DRG. Two new policy statements were issued on May 1, 1969 as a result of these deliberations, one each for the intramural and extramural programs.

The Division has recently initiated detailed followup of Institute and Division handling of review groups' concern for apparent hazards or unethical procedures in certain research projects.

Uncertainties following the 1968 reorganization of the NIH delayed the Division's production of publications on the programs for which it has central service responsibility. By the end of the calendar year, the Division hopes to be in a position to distribute up-to-date information on these programs at scientific meetings and in response to inquiries about NIH research program support.

Division of Research Services

The broadened responsibilities of the Division of Research Services focused attention in fiscal year 1969 on the need to separate intramural technical support from engineering, construction and maintenance functions. To facilitate direction and progress of NIH construction and, at the same time, provide an opportunity within DRS for increased concentration on the needs of bench scientists, a new organization, the Office of Engineering Services, was created under the Associate Director for Administration, NIH. All DRS activities relating to building design, construction, and maintenance were transferred to the new office. The activities remaining in the DRS include biomedical engineering and instrumentation, environmental services, medical arts and photography, production and distribution of research animals and media, and medical library services.

CONSTRUCTION

Construction of large projects administered by the Public Buildings Service, General Services Administration, tapered off during the latter part of fiscal year 1969. Construction of the General Office Building Extension, Building 31C, and the Cancer, Neurology-Mental Health and Cafeteria Buildings, were completed during the year.

Almost all work under Phase I of the Master Utilities Extension program was completed. The NINDS-NICHD Experimental Facility at Sabana Seca, P.R., is substantially complete. Alterations and additions to a number of the existing buildings were effected under separate contract.

The engineering design program includes 14 projects in various stages of planning and design. Also included are designs for alterations, plant maintenance and repair, and improvements to existing facilities.

ANIMAL PROGRAMS

Emphasis was placed on data processing of production and animal issue information. The pricing structure of animals was expanded to bring prices more in line with cost. Programs to improve the quality of animals for intramural research were continued and intensified. For the second successive year, rodent and rabbit colonies experienced no outbreaks of disease. A program was initiated to establish rat colonies in barrier environment and thereby permit production of rats free of chronic respiratory disease.

A nutrition laboratory was established to provide more intensive research on animal foods, and food specifications were revised. The colony of blood donor dogs was expanded and this reduced the number of dogs required for research by 1,300 animals.

BIOMEDICAL ENGINEERING

The Biomedical Engineering Branch professional staff was involved in approximately 180 research and development projects, many of which required an increase in the level of sophistication of technical collaboration and support provided. The year has seen noteworthy original contributions in the areas of prostheses, materials, laser technology, mechanization, automation, physiological monitoring, patient care, and physiological systems analysis. The technical services sections—Instrument Fabrication and Systems Maintenance, achieved productivity peaks during fiscal year 1969. These sections performed 12,000 assignments during the year at a value of $1,000,000, an increase of 4 percent in jobs and 6 percent in dollars over the previous high, reached in fiscal year 1968. The concept of satellite operation has been enhanced in substance. One new satellite, located in the National Cancer Institute, Building 37, has been established. Planning for a satellite for the proposed new National Institute of Child Health and Human Development complex has been initiated and a potential technical support unit for the National Cancer Institute-Baltimore Cancer Research Center is under discussion.

ENVIRONMENTAL SERVICES

This branch was reorganized on the basis of functional programs one year ago. In the past year emphasis was placed on better programing of activities. As an important part of the biological hazards control activities, assistance was given to a joint National Cancer Institute-DOW Chemical project in evaluating Building 41 construction details, testing barrier components and training support service personnel who will occupy the building. The development of improved hood systems for hazardous laboratory projects has increased the equipment evaluation workload of the branch. Inadequate air flow and continued problems with filter systems emphasize the need for stepped-up surveillance in the Institute laboratories.

The Fogarty International Center

The John E. Fogarty International Center for Advanced Study in the Health Sciences was established at NIH on July 1, 1968. Named in honor of the late Congressman Fogarty, who was vitally interested in health and biomedical research, the Center establishes a locale within the Government for serious thought and discussion by outstanding scholars of the implications of advances in biomedical research.

SCHOLARS-IN-RESIDENCE

The Scholars-in-Residence Program is designed to facilitate the work of individual scholars and the exchange of ideas among distinguished science leaders, and promising young scientists.

Individuals accepting an invitation to participate will be known as "Fogarty Scholars" during their period in residence. Invitations will be extended to persons of distinction who have the educational and cultural background and research experience to make significant contributions in the health sciences. Awards will be made without regard to national boundaries.

Participating scholars probably will not exceed 10 at any one time and their period of residence will vary from 3 to 12 months.

Invitations were extended during the fiscal year to the first group of seven scholars. The first scholar will join the program in October 1969, the remainder will arrive between January and May, 1970.

CONFERENCE AND SEMINARS PROGRAM

By virtue of the international reputation for scientific excellence enjoyed by the NIH, the Fogarty Center can draw upon resources of the international bimoedical research community for its Conference and Seminar Program. The objectives of this program include:

a. To promote advanced study in the health sciences;
b. To identify the legal, ethical, social and economic problems that may arise from new findings of biomedical research;
c. To advance understanding and insight into these problems through cross-disciplinary conferences and seminars,
d. To stimulate research in particular fields.

To accomplish these objectives, two types of meetings will be held. A series on biomedical science will be related to NIH research. The Center also will conduct meetings to consider matters involving science policy. The population field will be covered in collaboration with the Center for Population Research, National Institute of Child Health and Human Development. Interest also has been expressed in considering the progress being made in applying genetics to human problems and in the implications for social change in the rapid increase of the technical abilities of human geneticists. With the increasing pace of research in molecular biology, there appears to be some prospect, for example, that within a generation biological engineering will be possible, so that metabolic defects can be repaired.

Three conferences were held in fiscal year 1969. The first was a Colloquium on the Reform of Medical Education. Twenty-five educators, researchers and medical students from 10 countries spent 3 days discussing the reorganization of medical schools in the advanced countries of the world.

The second was an International Symposium on Environmental Influences on Genetic Expression cosponsored with the National Institute of Child Health and Human Development, in which scientists from many disciplines met to identify critical pre- and post-natal periods in the development of a child. The third conference, the Sixth Colloquium on the Pupil (Eye), cosponsored with the National Institute of Neurological Diseases and Stroke and the National Eye Institute.

INTERNATIONAL VISITORS CENTER

The third new activity of the Fogarty Center is the establishment of an International Visitors Center. This center will be the focal point at NIH for the reception of international dignitaries and scientists, who number several thousand each year. Building 16A, adjacent to Stone House, is being renovated to house the center and will be open in July 1969.

INTERNATIONAL POSTDOCTORAL FELLOWSHIP PROGRAM

Two existing programs were transferred from the former NIH Office of International Research. The first of these is the International Postdoctoral Fellowship Program. Under this program, young scientists from 40 foreign countries come to the United States for one to two years of advanced research training. Fellows are required to return to their home countries at the end of their fellowships. Followup surveys have indicated that a majority of Fellows continue to work individually and in collaboration with former preceptors on research projects of interest to the United States after their return home, and thus contribute to the health of the American people. In fiscal year 1969, 104 new fellowships and 69 second-year fellowships were awarded. Total cost of the program was $1,409,102.

SPECIAL FOREIGN CURRENCY PROGRAM

The second program transferred is the Special Foreign Currency (Public Law 480) Program. U.S.-owned foreign currency is made available to the NIH to fund collaborative research projects of interest both to the United States and to the foreign government involved. The

Fogarty International Center administers the NIH-portion of this program.

In one Public Law 480 project, during extensive studies on vitamin A metabolism in undernourished preschool children, scientists in Vellore, India demonstrated unequivocally that injection of a single large dose of vitamin A *in oil* in children *on marginal diets* does not prevent vitamin A deficiency and its sequellae (which may include blindness). These scientists have also shown that injectable vitamin A *in oil* is prophylactically inactive in children with frank kwashiorkor, a disease produced by severe protein deficiency. In contrast, injection of water-soluble vitamin A is highly effective. These findings are being communicated as widely as possible since in many areas the injection of vitamin A *in oil* is used as a prophylactic measure.

Bureau of Health Professions Education and Manpower Training

The Bureau of Health Manpower was expanded in January 1969 and renamed the Bureau of Health Professions Education and Manpower Training. Its seven divisions are divided into two categories—Institutional Development and Health Manpower Development. Now consolidated within the Bureau are all construction grant functions, including the health research facilities functions of the former Division of Research Facilities and Resources, and the construction grant functions of the National Library of Medicine.

During the past year, the Bureau continued to—

- Assist in the development and construction of new institutions and new programs, and in the expansion, rehabilitation and maintenance of existing institutions engaged in the education and training of health personnel;
- Provide assistance to students attending these schools, and
- Encourage schools to develop new methods of teaching and curricula for new types of health personnel.

Appropriations in fiscal year 1969 totaled $93.2 million in construction grants and $248.4 million for all other programs, compared with 1968 appropriations of $238 million for construction and $226.9 million for other purposes.

Division of Allied Health Manpower

The Division of Allied Health Manpower is the focus for programs that provide support for the education and training of manpower in allied health, public health, and certain other health occupations and specialties.

The Division provides extensive consultation to junior colleges, colleges, and universities in developing educational programs to meet health manpower needs.

BASIC EDUCATIONAL IMPROVEMENT

In fiscal year 1969, 258 junior colleges, colleges, and universities were awarded grants totaling $9,750,000 for the improvement and strengthening of allied health curriculums. Because of an increase of 28 schools eligible for awards under this formula grant program while the amount of funds available remained the same as in fiscal year 1968, the level of funding decreased from nearly 96 percent to 78 percent of each institution's entitlement.

ADVANCED TRAINING

During the year, 397 trainees preparing to teach or to serve in administrative, supervisory, or specialist capacities, enrolled in 62 institutions, received traineeships totaling $1.5 million. Approved but unfunded applications represented an additional 51 trainees.

NEW METHODS AND CURRICULUMS

Projects for development, demonstration, and evaluation of new methods and curricula for training technologists and technicians are supported by Developmental Grants. The 16 projects first funded in fiscal year 1968 were awarded continuation grants totaling $1.2 million.

CONSTRUCTION OF TEACHING FACILITIES

Five grants totaling more than $3 million were awarded for construction of allied health professions teaching facilities, which will create 799 student spaces.

PUBLIC HEALTH TRAINING

Over 13,000 students received a total of $7.9 million in public health training.

Institutional grants for curriculum development totaled about $9.5 million. About half of the total was awarded on a formula basis to the 15 schools of public health. The remainder was awarded for 117 special projects through which, it is estimated, about 7,000 students received instructional benefits.

ALLIED HEALTH EDUCATIONAL PROGRAMS INFORMATION

The Division initiated projects to develop national directories of educational programs. The American Association of Junior Colleges and the Association of Schools of Allied Health Professions, were awarded contracts for this purpose.

Division of Dental Health

Charged by law to promote higher standards of oral health for the American people, the Division of Dental Health seeks practical ways to advance the education, training, and use of dental manpower; to extend and improve community dental services, and to develop and apply methods of preventing and controlling dental disease.

MANPOWER DEVELOPMENT

The shortage of dentists and their auxiliaries is increasing and is already acute in some areas. Since 1965 the Division has cooperated with the American Association of Dental Examiners to develop a National Data Compilation System on Dental Manpower, including dentists, dental hygienists, and dental assistants. By the end of the fiscal year, the State Dentist Manpower Reports, summarizing the personal and professional characteristics of dentists licensed in 48 States and the District of Columbia, were completed. In addition, handbooks of statistics on dental hygienists are being compiled from a survey made last year. Plans have been made, and a questionnaire designed, for a pilot study of dental assistants.

The Division continued to collect and analyze data from a study to increase dental productivity by expanding the functions of chairside dental assistants. The study at the Dental Manpower Development Center, Louisville, Ky., is scheduled for completion in fiscal year 1970. A preliminary report revealed that the productivity of two dentists, each working with a team of four trained clinical dental assistants together with supportive staff, increased 140 percent over the productivity of the same two dentists working with two conventional dental assistants.

Manuals containing guidelines for the development of dental hygiene and dental assisting teaching programs have been developed. A manual is being prepared for training students in dental laboratory technology. Efforts are under way, through contract support, to increase the number of dental auxiliary educators. Short-term training programs, particularly for dental hygienists, have been supported.

Approximately 9,000 students in 49 dental schools received dental auxiliary training. Grants totaling $3,200,000 were awarded, the largest amount in the history of the program.

Research projects aimed at improving dental education and methods of recruiting into the dental profession are being conducted in several areas. The merits and practicality of the total patient care concept were tested at the University of North Carolina. At the University of Iowa, an experimental self-instruction cubicle was designed, constructed, and evaluated.

The Division is endeavoring to make continuing education accessible to all practicing dentists by means of grants, contracts, and the development and demonstration of education courses. Five grants for research in continuing education were awarded and a contract was awarded for a prototype continuing education system for the state of Idaho.

Two prototype courses demonstrating programed group-teaching machines and one information film were presented in 19 States and Canada to 4,831 participants.

Fifteen new applications were received for research fellowships and six were approved; two of these have been awarded while the remaining four await funding. The program supports five predoctoral Fellows and six special Fellows.

Two research training grants were awarded during the year. As of June 30, 1969, there were five active training grants totaling $450,000. Fifteen postdoctoral and five predoctoral trainees are participating.

DISEASE PREVENTION AND CONTROL

The Division gives high priority to programs of prevention and control of dental diseases. Strong support is given to fluoridation since this proven health measure could safely reduce children's tooth decay by up to 65 percent.

By the end of 1968, 52 percent of the population received the benefits of fluoridation. Consultation was provided to communities desiring to fluoridate their public water supplies. In fiscal year 1969, at least 75 percent of the requests for information on dental health matters was related to fluoridation. To respond to frequently asked questions, the Division published the *Fluoridation Census-1967*, listing communities in the United States with controlled fluoridation of water supplies. A more recent publication, *Natural Fluoride Content of Community Water Supplies*, lists communities with water supplies having a natural fluoride concentration of 0.7 part per million or greater.

The Division also provided assistance and consultation in developing dental care for 2,500 Head Start projects, 118 Job Corps Centers, 47 Neighborhood Health Centers and VISTA training centers.

In connection with Head Start, a project in Berkeley Unified School District (California) will develop an elementary school program in dental health education. In Minnesota, a project will test feasibility of a high school program in preventive periodontics. A dental health education film, "An Ounce of Prevention," was produced under a $36,578 Division contract cooperation and shown on the 161-station National Educational Television network.

APPLIED RESEARCH

Two research accomplishments in periodontal disease were (1) completion of a 3-year clinical study to determine the effects of good oral hygiene on periodontal health, and (2) the completion of two short-term studies to evaluate different toothbrushing methods to remove plaque from teeth. Findings of these are expected to provide a research base for a nationwide attack on periodontal disease, the main cause of tooth loss after age 35.

Approximately 6,000 children are born every year with cleft lip or palate. Some studies to determine possible causes of these deformities have been completed. These investigations reveal possible seasonal variation in births of afflicted children, and certain increases in cleft lip incidence among births that followed outbreaks of A2 influenza.

Work continued on applied clinical studies of dental filling materials and techniques. Approximately 700 pairs of dental restorations were placed for study and studies of intermediate restorative materials and of fluoride-treated dental amalgam were initiated in Metlakatla, Alaska.

There were 38 active applied research projects supported for a total of $1,259,000. More than a dozen scientific publications resulted last year from research projects sponsored by the Division. A Conference on Clinical Testing of Cariostatic Agents, sponsored by the American Dental Association was partially supported by a Division research grant.

DELIVERY OF DENTAL SERVICES

More efficient ways of providing dental services are of interest to the Division.

Studies sponsored by the Division show that school children, under the supervision of their teachers, can successfully self-apply cleaning pastes and mouthrinses containing fluorides. Preliminary results suggest these treatments are effective in reducing dental decay among the children.

The Division has contracted with the Tennessee Department of Public Health to conduct a pilot study of the dental needs of disadvantaged children in seven counties in the Chattanooga area. Information collected is expected to provide a basis for planning a national children's dental care program. The first round of treatment was completed this year for about 2,500 first-grade students.

At its Dental Health Center in San Francisco, the Division is investigating the potential hazards of airborne bacterial exchange between patients and dentists during treatment procedures.

The Division fosters the development of programs of prepaid dental care by providing consultative services, technical assistance, and information material, including *The Directory of Prepaid Dental Care Plans–1967*, published this year.

A Guide to Federal Financial Aid for Dental Health, covering a wide range of dental activities also was published.

Division of Educational and Research Facilities

The Division of Educational and Research Facilities, one of the new components of the Bureau, was established January 4, 1969, to bring together in one unit all NIH extramural construction grant programs.

HEALTH RESEARCH FACILITIES

The Health Research Facilities Construction Program supports grants for new construction, remodeling, and/or equipping facilities. In fiscal year 1969, 19 grants totaling $21,433,128 were awarded.

HEALTH PROFESSIONS EDUCATION FACILITIES

The Health Professions Educational Assistance Program assists institutions through matched fund grants to construct new schools and expand or modernize existing schools, making it possible to increase the number of students of medicine, dentistry, pharmacy, optometry, nursing, osteopathy, public health, podiatry, and veterinary medicine.

Since its enactment in 1963, the program has awarded more than $500,000,000 making possible addition of 4,791 new first-year student places in 133 schools.

During fiscal year 1969, awards totaling $130,431,760 were made to 16 schools, to create 592 additional first-year student places.

NURSE EDUCATION FACILITIES

This program provides matching grants to construct, expand or remodel facilities for nurse education to accommodate an increased enrollment and improve training programs.

During the year 33 programs received construction awards totaling $20.6 million to add 1,471 first-year places for students of nursing.

Including all awards, as of June 30, 1969, Federal funds had provided $81.8 million to construct or remodel facilities for nurse training, enabling 140 schools to expand enrollment by 5,860 first-year student places.

ALLIED HEALTH FACILITIES

Junior colleges, colleges, and universities with professional or technical training programs are eligible to apply for matching grants. During the year, five construction grants were awarded totaling $3,008,080. These funds will provide facilities for 648 additional students.

MEDICAL LIBRARY FACILITIES

Under the construction authority of the Medical Library Assistance Act of 1965, three grants totaling $1,250,000 — two for new facilities and one supplemental grant — were awarded during the fiscal year. The awards made possible the addition of 40,000 net square feet of space to accommodate 200,000 volumes, an increase of 100,000 volumes.

Division of Health Manpower Educational Services

HEALTH PROFESSIONS EDUCATIONAL IMPROVEMENTS GRANTS

Health professions basic educational improvement grants, totaling $33,636,000 were awarded in 1969 to 172 schools to improve the quality of their programs.

Health professions special educational improvement grants, totaling $32,364,000, were awarded to 103 schools of medicine, dentistry, optometry, osteopathy, and podiatry.

Table 3.—*Health professions educational improvement grants in fiscal year 1969*

Type of school	Basic grants		Special grants	
	Number	Amount	Number	Amount
Medicine	100	$21, 123, 000	60	$19, 783, 689
Dentistry	51	9, 213, 000	26	8, 722, 630
Optometry	10	1, 480, 500	8	1, 685, 485
Osteopathy	6	1, 126, 000	4	1, 118, 612
Podiatry	5	693, 500	5	1, 053, 584
Total	172	33, 636, 000	103	32, 364, 000

STUDENT ASSISTANCE

More than 52,000 students in 938 schools of medicine, dentistry, nursing, optometry, osteopathy, podiatry, pharmacy, and veterinary medicine were assisted by Health Professions Student Loan and Scholarship Programs.

Table 4.—*Student assistance program in fiscal year 1969*

	Nursing student loans	Health professions student loans	Health professions scholarships
Number of participating programs or schools	694	231	244
Total amount allocated	$16, 007, 807	$26, 429, 000	$11, 218, 817
Total enrollment	112, 655	69, 393	59, 351
Student recipients (estimated)	27, 000	23, 000	13, 500

FOREIGN STUDENTS

Program and guidance services were provided to 479 new foreign students and 271 carryover students by the Foreign Students Education Program.

Division of Physician Manpower

In 1969 the number of active physicians in the United States was approximately 318,000, but this included those engaged in research, education, and administration. It is estimated that a need exists for

50,000 additional physicians to provide adequate health care to the people of the Nation.

The Division of Physician Manpower works with medical schools and other institutions to stimulate interest in augmenting the supply of physicians and improving their effectiveness.

PHYSICIAN EDUCATION

The Division provides professional review of all applications from medical and osteopathic schools for Special Project Grants (formerly Special Improvement Grants). Sixty-four schools of medicine and osteopathy have received support.

A contract-supported project for the retraining of inactive physicians was completed at Pacific Medical Center, San Francisco and the ensuing report will be made available to medical educators. Under a contract with Bowman Gray Medical School a program has been started to train "assistants to the physician," with particular reference to the field of pediatrics.

Medical educators at Ohio State University College of Medicine are evaluating a self-instructional program that will allow medical students to pace their studies individually throughout much of the curriculum.

CONTINUING EDUCATION

The "information explosion," coupled with increasing demands for high quality medical care, has stimulated many physicians to continue their education. The Division focuses on improving the quality and availability of continuing education programs.

A study at the University of Wisconsin is being completed in which individual programs under a preceptor have been designed for each practicing physician in accord with the demands of his practice.

From the San Francisco Medical Center of the University of California, faculty members become physicians-in-residence at neighboring community hospitals for several days each year to teach and evaluate continuing education programs. The exchange of information which has resulted has been of benefit to both the practicing physicians and to the faculty. The latter are enabled to relate the education of medical students to the environment in which they will be practicing.

PHYSICIAN RESOURCES

The Physician Resources Branch provides a national clearinghouse for information concerned with the supply, distribution and availability of the Nation's medical and osteopathic schools, students, graduates and physicians.

Data on "How Medical Students Finance Their Education" has been collected and tabulated. The text is in preparation for publication.

PROFESSIONAL ACTIVITIES

Within the Professional Activities Branch, a study will be continued to determine what effect Public Law 89–97 (Medicare and Medicaid) and related socioeconomic developments are having and will have on teaching hospitals. Also, in cooperation with the St. Louis (Mo.) County Health Department, the Division is assessing the demands for health services by various societal groups in a suburban community. This is similar to the University of Kentucky study of a rural community, Menifee County, and to a study to be conducted by Mt. Sinai Hospital, New York City, of the inner city ghetto in both of which the Division plays a supportive role.

In collaboration with the Division of Allied Health, the Division supported at Emory University an analysis of anesthesiologists. Levels of professional proficiency have been categorized, and an anesthesiology manpower model is now being developed.

A 3-year grant for $160,000 was awarded to the University of Utah to investigate factors in the background of medical students which may predict their later performance as physicians.

Division of Research Resources

The Division of Research Resources supports resources within institutions that are essential to biomedical research and to scientific progress. The Division provides assistance on a nationwide basis for general clinical research centers where new diagnostic and treatment techniques are developed; primate centers for the study of human diseases using primates; animal resources vital to progress in medicine, and special research resources with sophisticated and expensive instruments and instrument systems. The Division also provides general research support grants to help institutions maintain and improve research capabilities.

SPECIAL RESEARCH RESOURCES

Special research resources are designed to bridge the gap between the physical and biological sciences. There are 59 of these, which fall into three major areas: 47 computer centers; nine biochemical instrumentation centers, and three biomaterials preparation centers.

Computer-based mathematical models have proved to be a powerful research aid in biochemistry as a result of work performed at one computer resource. A unique programing system has been developed that enables "computer-naive" scientists to build complicated models of biochemical systems. Interplay between computer predictions and laboratory results has revealed much about the basic machinery of living cells.

Another computer resource is developing a technique to measure blood flow in any organ system. It is now possible for surgeons to relieve localized arteriosclerotic obstruction in the arteries of the heart. This new technique can be used to measure blood flow in the heart arteries and determine which vessels need attention.

A collaborative program at a mass spectrometry resource is testing existing methods to detect and identify drugs, poisons, and their breakdown products (metabolites) in body fluids. One of the goals of the research is to test feasibility of employing the technology routinely in patient care, particularly in emergency situations.

GENERAL CLINICAL RESEARCH CENTERS

The 93 clinical research centers supported by the Division provide only a small portion of beds in American hospitals, but they exert a vital influence on the practice of medicine in the United States. The 1,000 clinical center beds set aside exclusively for research are distributed through university hospitals containing more than 60,000 beds. In this setting, they aid scientists in introducing new and advanced approaches to diagnosis and treatment. The advances and accomplishments achieved in this nucleus are brought to bear on the practice of medicine in the 580,000 beds in 3,700 hospitals that provide most of the inpatient care for acute illness in the United States.

Clinical research centers are provided with the equipment necessary to conduct research and are staffed by personnel with special training.

Many small, prematurely born or critically ill infants, especially in poor families, cannot be fed by conventional methods because they are too immature or too ill to coordinate their sucking and swallowing reflexes. To alleviate this problem, one center developed a relatively simple surgical procedure for placing a feeding tube directly into the infant's stomach. This procedure allows critically ill infants to get adequate nutrition and helps prevent complications.

Investigators at clinical research centers have made several important findings about the effects of oral contraceptives. As the hormone content of these drugs has been reduced in order to avoid undesirable side effects, an increasing number of women have conceived even though taking "the pill." Current studies indicate that a common sedative inhibits the action of the drug. These findings suggest that women taking the sedative, or, for that matter, other types of medication, may find "the pill" ineffective in preventing pregnancy.

Osteoporosis, the weakening of bones in the aged, has until recently been unresponsive to treatment. At one clinical research center, patients on low dosage regimens of sodium fluoride for one to six years have shown significant improvement in their bone condition.

Clinical research centers have long been involved in transplantation. One of the early significant uses of the centers was for kidney transplants. Of the four most active heart transplant teams, three use clinical research centers extensively. The majority of the liver transplants performed thus far have been in clinical research centers. At present, many centers are involved in transplantation research ranging from basic immunology and development of new surgical techniques to new treatments to ensure graft longevity.

ANIMAL RESOURCES

The Animal Resource Program assists institutions increase and improve their laboratory animal facilities and resources. Seventy projects are currently supported.

Today, there is growing recognition that the care of laboratory animals is an institutional responsibility as well as one of individual scientists. In addition, the Laboratory Animal Welfare Act (Public Law 89–544) stimulated increased demand to improve facilities and care. At present, the Animal Resource Program is assisting 17 institutions in accomplishing this goal. Grants provide funds for equipment such as cages and cagewashers; for minor renovations to facilities; for support of professional and supervisory personnel, and support of clinical laboratories to improve animal health.

An important facet is definition of new animal models of human disease. During the year, a $20,000 grant was made to develop and maintain a colony of hemophilic beagles. Classic hemophilia (delayed clotting of the blood) in these animals is pathologically, genetically, and hematologically indistinguishable from that in man. Recent spleenic transplants from normal dogs to the hemophilic dogs suggest that the spleen is the main site of synthesis of the anti-hemophilic factor.

In addition, a resource for culture collections of algae strains has been supported. New algal strains have been isolated and characterized for their use in genetics, differentiation, developmental biology, ecology, and physiology. Over 11,500 strains are maintained.

Seven regional primate research centers provide facilities, on a nationwide basis, for teams of scientists to conduct intensive research on man's closest animal relatives, the subhuman primates.

During the past year, approximately 20 percent of primate center research was on mental retardation. At one center, for example, preliminary findings on the consequences of prenatal and neonatal thyroid deficiency have contradicted the view that thyroid hormones are essential for normal physical development prior to birth. Rhesus monkey offspring of mothers without thyroid glands, and having no thyroid glands themselves, showed no abnormalities in physical appearance.

They did, however, display severe mental retardation, showing the importance of the gland to mental development.

At another center researchers are trying to develop a vaccine against the herpes virus.

GENERAL RESEARCH SUPPORT

The General Research Support Program is designed to strengthen the overall capacity of institutions to perform medical and health-related research and research training. Grants enable institutions to exercise greater initiative and control over the emphasis, direction, content, and quality of their entire research effort. The program is composed of three elements: general research support; biomedical sciences support, and health sciences advancement awards.

During fiscal year 1969, $48.2 million was distributed to 330 institutions as General Research Support Grants. Of this total, $25.4 million went to medical schools. The next largest category, hospitals, received $8.5 million.

An investigator at one institution developed a new tissue typing technique to match donor and recipient for organ and bone marrow transplants under general research support funding. As a result, a 2-year-old boy with a rare genetic defect received successful bone marrow transplants from his 9-year-old sister. As with transplants of other organs, bone marrow transfusion raises the possibility of serious graft-versus-host reactions. The transplant team reasoned that this could be avoided if donor and recipient were closely matched. Research with animals, funded by general research support, had shown that the new tissue typing technique was valid. Later, the test was used successfully with renal transplants. Finally, it was used in the bone marrow transplant.

The Biomedical Sciences Support Grant extends support of the institutional grant to the non-health components of academic institutions, provided that these components engage in biomedical research and research training. In fiscal year 1969, $75 million was appropriated for this program and awards were made to 110 institutions.

Health Sciences Advancement Awards help academic institutions strengthen their activities in health sciences. They provide funds annually, usually for 5 years. Awards are competitive on the basis that applicant institutions must identify and describe a unifying research theme within the institutional proposal for which funds are requested. The 1969 appropriation of $5 million permitted two new awards, bringing the total to 11.

Division of Nursing

The Division of Nursing concerned itself with the changing role of nursing, the administration of the Nurse Training Act of 1964, planning for new programs authorized by Title II of the Health Manpower Act of 1968, studies and projects to improve the production of nurses, the utilization of nurse manpower, and the quality of nursing service, and consultation to help public health agencies, schools of nursing, patient-care institutions, and planning groups provide better nursing care.

NEW IMPROVEMENT GRANTS

New projects for improvement in nurse training which the Division supported show concern with the clinical care of patients and with educational oportunities for nursing personnel. Hunter College of The City University of New York is conducting a 17-month experimental work-study program to prepare licensed practical nurses in the city's public hospitals for service as registered nurses. Wayne State University in Michigan is conducting a 2-year graduate course to prepare health nurse clinicians with strong capabilities in public health, medical-surgical nursing, and guardianship of essential continuity in health services. A grant to a Niagara University School of Nursing in New York State provides for construction of a simulated hospital unit equipped with a cardioscope and a cardio-trainer.

Under a recruitment contract, the California State College at Los Angeles Foundation is identifying Mexican-American high school students with potential for nursing and encouraging them to undertake initial nursing education. To overcome language barriers, the project is employing bilingual staff.

HEALTH MANPOWER ACT OF 1968

The Health Manpower Act, which became effective July 1, 1969, has made agencies eligible for project grants to improve nursing education, to plan or establish additional nursing education programs, and to help nursing education programs attain accreditation, conduct educational research, or expand enrollment.

IMPROVEMENT OF NURSING PRACTICE, NURSE MANPOWER, NURSE UTILIZATION

Other activities of the Division included renewed measures to bring inactive nurses out of retirement, epidemiological studies, and seven contracts for studies of impeding factors in nursing education, nursing education costs, the changing role of the nurse, and automation to improve nurse utilization.

Agencies in 31 States continued, with Division Contract Support, to stimulate inactive nurses to retrain. From July 1968 to April 1969, an additional 2,479 nurses had completed refresher training; one-half of these already returned to practice.

Studies to improve care to hospital patients continued at the Division's Nursing Research Center in California. In the belief that nurses should be relieved of nonnursing activities, the center has been developing a unit manager system to release nurses for direct patient care, and guidelines to help hospitals convert to the unit manager system.

The Division, in cooperation with the National League for Nursing, developed a nursing record which incorporates the Division's methodology for reporting the needs and progress of patients receiving public health nursing care. After testing in over 50 service agencies, the League is now making this record form available to public health agencies throughout the country.

The Division is supporting the evaluation of a 16-month graduate experimental program to prepare pediatric nurse practitioners—a new category of nurse specialist competent to act independently in certain areas.

RESEARCH PROJECT GRANTS

The Division continued to communicate research information by supporting three conferences: the 2nd Annual Western Research Conference; the 5th Annual Research Conference of the American Nurses' Association, and a Nursing Theory Conference.

The nursing staff worked with its Review Committee on Research in Nursing in Patient Care on two areas: (1) establishment of guidelines for new grant mechanisms for the research and research development, and (2) critical appraisal of the status of research in nursing.

RESEARCH TRAINING

The Division supported 122 Predoctoral Nurse Fellows in research training at 44 institutions of higher learning, and one Postdoctoral Fellow. Institutional grants for Nurse Scientist Graduate Training, were made to 36 graduate departments in eight universities for doctoral training of 84 trainees.

More generous funding of the extramural research and research training programs could have resulted in greater gains. Progress has been impeded because research and research training costs have increased while appropriations have remained stationary. Awards for research project grants dropped from 60 to 53 in fiscal 1969. New projects dropped from 22 to 16. Although four applications for Nurse Scientist Graduate Training Grants had been approved, only one additional program could be funded.

PLANNING

On request, the Division provided consultation to the planning groups of seven States, the District of Columbia Metropolitan Area, the region of Northwest Ohio, and the Commonwealth of Puerto

Rico. Consultation for revising public health nursing curricula was given by the Division to nursing faculty in 13 universities.

Division of Nursing consultants assigned to the Regional Offices of the Department of Health, Education, and Welfare have contributed consultation services to the Housing and Urban Development agency; participated in comprehensive health planning and implementation of Regional Medical Programs, and helped to draw up standards of care for patients in nursing homes.

National Library of Medicine

Over recent years the National Library of Medicine has modified its traditional library functions, and has become a focus for the application of contemporary communications technologies to support the national health effort. The Library is organized into five subdivisions: Library Operations, Extramural Programs, Specialized Information Services, the National Medical Audiovisual Center, and the Lister Hill National Center for Biomedical Communications. In addition, an Office of Computer and Engineering Services (OCES) provides support in information storage and retrieval.

LIBRARY OPERATIONS

During this fiscal year Library Operations and OCES continued to expand the services of NLM's computer-based Medical Literature Analysis and Retrieval System (MEDLARS), which has been operational since 1964. With the establishment of ten MEDLARS centers and eight Regional Medical Libraries, a library network now provides rapid and efficient services and resource sharing throughout the United States. MEDLARS centers in the United Kingdom, Sweden, Australia, and France, provide international links.

At NLM, over 6,400 individual computer searches were performed in fiscal year 1969, and approximately 16,000 searches through the MEDLARS network. In response to requests from health professionals throughout the world, the Library sent out 23,005 Literature Searches (reprints of individual computer searches). In addition to *Index Medicus*, the system is now producing 16 indexes of current bibliographic information for specialty groups such as dentists, epidemiologists, and neurosurgeons.

By the close of fiscal year 1969, citations to journal articles stored in the system's magnetic tapes approached the millon mark (997,812), making it one of the largest of its type in the world. Because the amount of input and output has now exceeded the original system design, several computer programs were modified to allow processing to continue until MEDLARS II becomes fully operational late in 1971.

A $425,000 contract was signed with Sanders Associates, Inc., for acquisition of a fully automated graphic image storage and retrieval system. This system will store microfilmed journal articles, and provide for automatic retrieval of enlargement prints of articles requested, for use in the interlibrary loan program. The equipment wll be installed in 1970.

EXTRAMURAL PROGRAMS

The Medical Library Assistance Act of 1965 enabled the Library in fiscal year 1969 to award $9,154,452 for the intiation or continuation of extramural programs. Grants were made for 17 graduate and postgraduate training programs for medical librarians and biomedical communication specialists (two new programs in fiscal year 1969) and for the support of more than 60 research projects related to biomedical communcation techniques and systems. Awards were made for construction of two new health science libraries. Fifteen new grants were awarded under the Resource Grant Program which has now improved resources and services in 389 libraries in medical schools, hospitals, and other health science institutions in 49 States.

Grants to establish Regional Medical Libraries were made to: (1) New York Academy of Medicine, serving New York and the northern half of New Jersey; (2) Emory University, serving Alabama, Florida, Georgia, Mississippi, South Carolina, Tennessee, and Puerto Rico; (3) Wayne State University, serving Kentucky, Michigan, and Ohio; (4) the John Crearar Library, serving Illinois, Indiana, Iowa, Wisconsin, and Minnesota, and (5) the University of California at Los Angeles, serving California, Arizona, Hawaii, and Nevada. Support continued for the Regional Medical Library programs at Francis A. Countway Library of Medicine (Boston), the College of Physicians of Philadelphia Library, and the University Health Sciences Library of the University of Washington (Seattle).

SPECIALIZED INFORMATION SERVICES

The Office of Specialized Information Servces is concentrating on planning, development, and operation of a national toxicological system, and improved availability of published information on the effects of drugs and chemicals on man, with advisory service from the Division of Medical Sciences of the National Academy of Sciences/National Research Council. The SIS staff initiated a set of 10 contracts totaling $868,000 for development of a national toxicological system.

NATIONAL MEDICAL AUDIOVISUAL CENTER

Despite budget restrictions, the Center produced several significant television series and motion pictures, conducted 149 consultations, surveys, seminars, workshops, and presentations, and distributed more than 75,000 audiovisuals. About 15,000 additional requests were not filled because of understaffing. NMAC furnished more than 7,100 references in the form of citations from the International Index of Medical Film Data.

The Center began a program of consultation and cooperation with the Veterans Administration to establish learning resource centers in VA hospitals.

LISTER HILL NATIONAL CENTER FOR BIOMEDICAL COMMUNICATIONS

The Lister Hill Center was established by Joint Resolution of Congress (Public Law 90–456), signed by President Johnson on August 3, 1968. The Center now operates under a Departmental Charter as the focal point for the development and coordination of communication networks and information systems to improve the delivery of health services, medical education, and medical research.

The Center has planned for the establishment of a biomedical communications network. Staff efforts have been concentrated on working with medical schools, hospitals, and professional societies, and with other Federal organizations.

NIH Grants and Awards By Institute or Division and Program, fiscal year 1969[1]

[Dollars in millions][2]

Component	Total Amount	Research grants[3]		Construction grants		Training grants		Fellowship and Traineeships		Research career program awards		Research contracts[9]	
		Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number[4]	Amount
Total	[5]$1,247.6	12,435	$627.6	77	$176.8	4,804	$278.0	4,061	$30.9	1,255	$28.0	1,199	$102.3
Research Institutes and Divisions	788.5	11,609	500.0			2,364	138.0	3,827	29.6	1,254	27.9	1,003	92.9
NIAID	73.1	1,349	50.1			174	9.4	168	1.5	118	2.6	138	9.5
NIAMD	110.8	2,437	83.2			315	16.0	306	2.9	156	3.8	74	4.9
NCI	130.4	1,228	73.0			214	11.7	234	2.1	98	2.2	367	41.4
NICHD	57.7	938	37.7			154	9.9	173	1.7	108	2.5	102	5.9
NIDR	21.4	285	13.8			106	5.3	77	0.8	51	1.0	16	0.4
NIEHS	12.7	117	8.1			48	3.6	16	0.1	4	0.1	13	0.8
NIGMS	143.6	1,486	73.7			624	46.6	2,080	12.9	393	8.4	21	2.0
NHI	131.5	1,837	90.1			398	18.8	220	2.1	210	4.9	142	15.7
NINDS	98.8	1,878	67.8			331	16.6	373	3.8	116	2.6	77	8.1
FIC	4.0	54	2.4					180	1.6			—	—
DBS	1.4											24	1.4
DRS, DRG, DCRT	6.9											8	0.9
OD, CC, JOINT	1.9											21	1.9
Bu. Health Prof. Educ. & Manpower Train	447.1	768	126.0	74	175.5	2,425	138.7	229	1.2	1	(6)	155	5.6
DAHM	13.1					320	12.6					7	0.5
DDH	6.0	34	1.3			57	3.9	12	0.1	1	(6)	31	0.7
DHMES	96.2					1,022	95.9	62	0.3			—	—
DN	51.5	56	2.6	33	20.6	1,018	25.9	140	0.6			80	1.7
DPM	135.6	11	0.9	21	133.4							24	1.2
DRFR/DERF/DRR[7]	144.7	667	121.3	20	21.5	9	0.4	15	0.1			13	1.5
Nat. Lib. Med	[5]12.1	58	1.6	3	1.3	14	1.3	5	0.1			41	3.7

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[1] Excludes scientific evaluation grants.
[2] Dollars may not add to totals due to rounding.
[3] Includes general grants-in-aid and research resource support grants.
[4] Each supplemental agreement involving funds is counted seperately.
[5] Includes $1.2 million for medical library resource and regional medical library grant programs.
[6] Less than $50,000.
[7] DRFR was transferred to BEMT in January 1969 and its functions divided between DERF (educational and research facilities) and DRR (research resources).
[9] Preliminary figures.

NIH APPROPRIATIONS,

[In

Activity	Total	General research and serv.	Allergy	Arthritis	Cancer	Child health	Dental
Total	1,394,052	84,809	96,841	143,888	185,150	73,127	29,984
Grants	833,314	71,041	68,087	117,953	98,546	57,364	22,860
Research grants	635,562	69,100	54,236	95,107	82,531	43,158	15,235
Research fellowships	56,362	1,615	4,362	6,737	4,374	4,193	2,015
Training grants	141,390	326	9,488	16,109	11,641	10,012	5,609
Direct operations	266,777	13,769	28,754	25,935	86,604	15,763	7,124
Direct research	86,648		15,079	14,905	16,483	6,543	4,728
Biometry & epidemiology	9,790			721	1,435	2,046	435
Collaborative studies	124,795	2,728	11,784	7,599	64,907	4,041	844
Biologics standards	8,499						
Training	1,026	187				89	
Review & approval	19,213	1,575	1,496	2,296	2,508	1,976	688
Program direction	8,130	1,204	395	414	1,271	1,068	429
International research	3,316	3,316					
Computer res. & tech	4,759	4,759					
International center	600						
Health Res. Fac	8,400						
Health Prof. Educ. & Manpower Training:	267,400						
Health manpower	172,176						
Dental Health	10,224						
Construction grants	84,800						
Loan funds	200						
National Library of Medicine	18,160						

NOTE.—Column figures do not add due to rounding.

fiscal year 1969
thousands]

Envir. health sciences	General medical sciences	Heart	Neurology	Biologics standards	Health research facilities	FIC	Bureau of Health Prof. Educ. and Manpower Training	Natl. Library of Medicine
17,820	163,513	166,927	128,934	8,499	8,400	600	267,400	18,160
12,498	154,938	128,840	101,188					
8,406	86,664	103,086	78,037					
200	21,373	7,604	3,889					
3,892	46,901	18,150	19,262					
5,322	8,575	38,087	27,746	8,499		600		
4,496		13,533	10,881					
		1,765	3,388					
	3,544	19,142	10,206					
				8,499				
	452	224	74					
439	3,156	2,593	2,486					
387	1,423	829	710					
						600		
					8,400			
							267,400	
							172,176	
							10,224	
							84,800	
							200	
								18,160

NIH Employment By Component, June 30, 1969

	Full-time
TOTAL	11,471
Office of the Director	1,925*
Allergy	695
Arthritis	615
Cancer	1,411
Child Health	400
Dental	291
Environmental Health Sciences	176
Eye	69
General Medical Sciences	191
Heart	564
Neurology	652
Clinical Center	1,476
Fogarty International Center	46
Biologics Standards	272
Computer Research and Technology	302
Research Grants	459
Research Services	616
Bureau of Health Professions Education and Manpower Training	832
National Library of Medicine	489

*Includes NIH Central Service Functions.

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